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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.

Life is Complicated... Let’s deal with it!

Arylsulfatase A
based on 1e1z.pdb
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Nitrophorin: Binding and Transporting Nitric Oxide
Audubon High School
Poster #1

Authors: Margarita Rojas, Iris Cruz, Lizette Olguin, Maritza Reyes, ZadaMae Zurheide, Maxx Giroux
Teachers: Brian Coffey
School: Audubon High School
Mentor: Peter Geissinger, Ph.D. and Department Chair, and Hannah E. Waggie, Ph. D. Candidate, University of Wisconsin Milwaukee, Department of Chemistry and Biochemistry

Blood sucking animals will often carry parasites that will infect millions of people each year, resulting in deterioration and sometimes death. When a parasite like the Kissing bug probes its host, it releases salivary proteins that may initiate a variety of allergic reactions in humans. These reactions can be moderate-to-severe, however they can also be life threatening if you don’t realize you have been bitten. Some blood sucking insects have salivary nitrovasodilators called nitrophorin that are unique heme proteins that serve as storage and delivery systems for nitric oxide (NO). Upon a bite from the parasite, the NO is transported to the bloodstream where it is released to bind with soluble guanylate synthase (sGC) which results in vasodilation and blocks blood coagulation. An additional function of nitrophorin, is the uptake of histamine to prevent the immune system from attacking the area. These two mechanisms of nitrophorin allow the insect to suck larger volumes of blood than it could otherwise. The NO is carried in the insect’s saliva, where it is at a pH of 5.0 until it is released in the host at the pH level of 7. Nitrophorin binds and transports NO, binding leads to changes in the protein, which prevent binding with other diatomic molecules such as O₂ and ensures delivery of NO at the appropriate time and location. NO binds in a linear geometry with iron at the center. Upon binding the distal pocket is buried, residues shifted toward the distal pocket allow Leucine 130 to pack against the NO molecule. The distal pocket leucines also wrinkle the heme found in nitrophorin’s center. The NO is then trapped by AB/GH loops. To further bury the bound NO, Val36 packs against Leu130 and Leu133. The new positions are stabilized through a hydrogen bonding network that involves Asp30, Glu32, Asp35, Asp129, and the N-terminus.

Modeling P2X4
Wisconsin Virtual Learning
Poster #26

Authors: Amber Wicklund, Catherine Minter, Chenoah Gad, Elizabeth Merkel, and Rachel Mangiulli
Teacher: Karen O'Donnell
School: Wisconsin Virtual Learning
Mentor: Andrew Karls, Ph.D. and Audra Kramer, M.S. Marquette University

To someone who has excessive P2X4 receptors, simple gestures like hugs could cause unbearable pain. P2X4, a protein receptor located on the membrane of neurons, plays a large role in neuronal communication and pain perception. Ion channels on dendrites, located on one end of a neuron, allow ions to enter, causing an electrical current that continues through the cell. Once a current reaches the axon terminals, neurotransmitters are released to the next neuron, opening more ion channels and allowing transmission of the signal. This relay between neurons causes the perception of pain. In its resting position, P2X4 is closed inhibiting ions to enter the neuron, signaling no pain. In order for the receptor to open, ATP acts as the neurotransmitter attaching to the binding site of P2X4. In some, repeated sensory injury can lead to a need for extra receptors to be produced leading to chronic pain. Current studies are finding ways to block ATP from binding to receptors, keeping the receptor closed. P2X4 consists of 3 units forming the quaternary structure of the protein and 3 binding sites allowing for ATP to attach, opening the structure. Wisconsin Virtual Learning’s SMART (Students Modeling A Research Topic) Team, using 3D printing technology, has modeled an open structure of P2X4, highlighting amino acids Leu 217, Leu 191, Lys 193, Lys 70, Thr 189, and Ile 232 from PDB file 4DW1. With more knowledge of P2X4, scientists can unravel the mystery of chronic pain. This program is supported by a grant from NIH-CTSA.
Modeling the Binding Site of α-bungarotoxin to Nicotinic Acetylcholine Receptors
Whitefish Bay High School
Poster #25

Authors: Jieun Heo, Rishika Joshi, Mary Claire Potter, and Michelle Shin
Teachers: Katie Brown and Paula Krukar
School: Whitefish Bay High School
Mentor: George Wilkinson, Ph. D., Concordia University Department of Pharmaceutical Sciences

Myasthenia gravis, a disease characterized by muscle fatigue and weakness, affects thirty million people a year. The venom of certain snakes generates a similar phenomenon in its prey, causing paralysis. In both cases, symptoms result from interference with neuromuscular transmission. In normal neuromuscular function, binding to acetylcholine creates changes in nicotinic acetylcholine receptors (nAChRs) that catalyze ion-selective transmembrane pore openings. The resultant ion flux enters the muscle cell via the neuromuscular junction, ultimately inducing movement. The Whitefish Bay High School SMART (Students Modeling A Research Topic) Team used 3D print technology to model the site where snake venom α-bungarotoxin (α-Btx) binds to nAChRs, located in a muscle’s plasma membrane at neuromuscular junction. Binding primarily takes place between the tips of nAChR fingers I and II, which form a mobile region essential for proper binding; and the C-terminal loop of α-Btx, loops A, B, and C; and the carbohydrate chain in the nAChR. The α-Btx residues Y93, Y190, Y198, and R149 are inserted into the aromatic cage of the receptor by R36 and F32 in finger II of α-Btx. This binding blocks the agonists’ access to the activation site. Thus, α-Btx prevents the opening of ion channels that allow the passage of electrical signals that induce movement. Further study of these ion channels and nAChRs as pharmaceutical targets could lead to medical breakthroughs in diseases such as myasthenia gravis, Parkinson’s, Alzheimer’s, and epilepsy.

Modeling the N-Terminal Domain of Cystathionine β-Synthase to Identify Mutations Correlated with Homocystinuria
Brookfield Academy Upper School
Poster #2

Authors: L. Ding, S. Gunadraj, T. Kaur, S. Kothari, E. Lenz, C. Lo, M. Morris, M. Morris, S. Mylavarapu, L. Wang
Teachers: Robbyn Tuinstra
School: Brookfield Academy Upper School
Mentor: Noah Leigh and Ramani Ramchandran, Ph.D.

Homocystinuria is an autosomal recessive disorder affecting approximately 1 in 350,000 people worldwide and is characterized by skeletal, nervous system, and vascular, abnormalities, such as delayed developmental milestones, myopia, and dislocation of the eye lens, osteoporosis, mental retardation, and increased risk of blood clotting. Major causes of homocystinuria are mutations in the enzyme cystathionine β-synthase (CBS), which catalyzes the condensation of serine and homocysteine to cystathionine, an intermediate in cysteine synthesis. CBS is a pyridoxal 5'-phosphate (PLP) and heme dependent enzyme regulated by S-adenosylmethionine (SAM). CBS is a homotetramer, each subunit consisting of distinct N and C-terminal domains. The N-terminal domain is the catalytic region, containing both the PLP and the heme cofactor, while the C-terminal domain is the regulatory region, binding SAM. Upon binding with SAM, the C-terminal domain is removed, and the enzyme functions as a homodimer. The PLP is covalently attached to CBS by lysine 119, while the heme is reversibly bound to CBS by coordination with cystine 52 and histidine 65. Over 150 mutations have been identified affecting the enzyme. These mutations primarily cluster around three areas of the enzyme: the heme binding site, the PLP and substrate binding active site, and the dimer interface. Homocystinuria can lead to several cardiovascular defects such as increased carotid plaque thickness, known as atheroma, in artery walls and intravascular thrombosis, the formation of a blood clot that obstructs blood flow through the circulatory system. A primary research goal is to understand how mutations in CBS, an enzyme found in muscle tissue, may lead to vascular abnormalities by identifying changes in embryonic vascular development in zebrafish (Danio rerio) lacking expression of the CBS-B isoform. Using 3D printing techniques, the Brookfield Academy SMART (Students Modeling A Research Topic) Team modeled the N-Terminal domain of the CBS enzyme, highlighting the heme and PLP coenzymes, along with various mutations associated with homocystinuria.
ACEing Radiation Protection:  
The Role of ACE Inhibitors in Mitigation of Radiation Damage  
Brookfield Central High School  
Poster #3

Authors: Max Czechowski, Adam El-Meanawy, Jialuo Gao, Jason Hubler, Tahmid Iqbal, Tarun Jella, Eugene Kim, Raga Komandur, Corey Li, Serena Nicoll, Hafsa Shereen, Zheng Yan, and Alice Zheng
Teachers: Ms. Louise Thompson
School: Brookfield Central High School
Mentor: Meetha Medhora, Ph.D, Medical College of Wisconsin

In 2001, the United States suffered a major terrorist attack that took the lives of thousands. There is a small, but real, risk of radiological attack or nuclear accident in the future. In addition, exposure of normal tissue to radiation poses a risk to cancer patients undergoing radiotherapy, as radiation induces the production of collagen. Grants were provided to our mentor to research ways to mitigate the harmful effects of radiation. Studies on radiation effects on rats have found that increased collagen is found in the interstitial space of the lungs, which limits free exchange of oxygen and carbon dioxide. Angiotensin Converting Enzyme (ACE) converts angiotensin I into angiotensin II, which binds to fibroblast receptors to produce collagen. By inhibiting the ability of ACE to convert angiotensin I into angiotensin II, the fibroblasts cannot produce the same levels of collagen. As a result, oxygen and carbon dioxide are more easily exchanged in the lung after damages from radiation. The beneficial effects of ACE inhibitors on the collagen buildup in the lungs have been observed in rats 7 months after exposure to radiation (Kma et al 2012). Understanding the collagen synthesis pathway by studying ACE and its inhibitors such as the commonly used drug lisinopril, may lead to the production of an efficacious treatment for radiation-induced fibrosis. The Brookfield Central High School SMART (Students Modeling a Research Topic) Team used the PDB file 1086 to create a 3D model of the protein ACE and investigate the interaction between ACE and the inhibitor lisinopril to better understand its molecular functions.

An Exciting ERα in Breast Cancer Treatment  
Westosha Central High School  
Poster #24

Authors: Julia Alberth, Nick Bielski, Jared Holloway, Julie Katzer, Mitchell Kirsch, Becca Lawrence, Maddie Murphy, Sheel Patel, Sean Quist, A.J. Reeves, Zack Wermeling, Julia Williams, Lucas Wysiatko
Teachers: Jonathan Kao
School: Westosha Central High School
Mentor: Oleg Brodsky BSc. MBA – Pfizer Inc.

According to the American Cancer Society, one in eight U.S. women will develop breast cancer in their lifetime. Strikingly, many of these women share a significant genetic commonality. It has been shown that many breast cancer patients test positive for high levels of Estrogen Receptor (ERα), a protein that regulates the differentiation and maintenance of neural, skeletal, cardiovascular, and reproductive tissues in their cells. ERα aids in the process of DNA transcription as a transcription factor. The activation of ERα occurs when a ligand, estradiol, diffuses through the lipid membrane and binds to the active site at the Ligand Binding Domain (LBD) while ERα is in the cytoplasm. Initially the LBD is inhibited by a chaperone protein, which immediately disjoins from ERα to allow estradiol to bind. The LBD is located at amino acid residues 303 to 552 highlighted in the model designed by the Westosha Central High School SMART Team using 3D printing technology. Afterwards, the complex is transported into the nucleus where the DNA Binding Domain (DBD) of the ERα protein binds to DNA and commences gene transcription. An overabundance of ERα leads to excessive transcription which may cause breast cancer. Therefore, in the treatment of breast cancer, inhibiting or degrading ERα is of immediate interest as a therapy.
Botulinum Neurotoxin Serotype A
West Bend High School
Poster #23

Authors: Savannah Kassin, Rebecca Fisher, Karl Vachuska, Rachel Monday, Erin Richards, Lily Miller, Logan Dommiss
Teachers: Judy Birschbach
School: West Bend High School
Mentor: Nicholas Silvaggi, Ph.D. University of Wisconsin-Milwaukee, Department of Chemistry and Biochemistry

USATODAY reports that the most toxic biological compound is used by 5.6 million people annually. The bacterium, Clostridium botulinum makes a toxin called botulinum neurotoxin (BoNT) (or BotoxA). Signs say BoNT may remedy ailments, but excess Botox can cause nerve damage and death. It is key to create a drug that can block BoNT’s effects if misused. BoNT enters motor neurons and interrupts nerve impulses, causing paralysis. The toxin consists of a heavy chain that is the targeting infiltration system, and a light chain is the warhead. When the light chain enters a motor neuron, it cleaves SNAP-25 at a Gln-Arg peptide bond, ending the nerve’s ability to release neurotransmitters. Vital for the toxin’s catalysis, key amino acids include His223, His227, and Glu262, which bind the Zn(II) ion. The Glu224 side chain joins in the BoNT catalytic machinery. Asp370 is essential for interacting with the Arg residue in the substrate’s scissile peptide bond. The BoNT/A active site can alter its structure to bind to unlike molecules: arginine and a hydrophobic cinnamic acid derivative. The West Bend SMART (Students Modeling A Research Topic) Team made a model showing how BoNT houses polar and hydrophobic molecules using 3D printing.

Myosin: The Cause or Solution for Coarctation of the Aorta?
Brookfield East High School
Poster #4

Teachers: Emily Barmantje
School: Brookfield East High School
Mentor: Dr. Thomas Eddinger, Marquette University

While more than 1 out of every 2,500 babies are born with a coarctation of their dorsal aorta (CoA), very little is actually known about the cause of this disease. It is hypothesized that the motor protein myosin may be one of the main determining factors of this birth defect. Decreased blood flow and high blood pressure above the coarctation are characteristics of CoA which causes the walls of the aorta to thicken. The cells in the thickened wall of the aorta express more nonmuscle (NM) myosin molecules and are less susceptible to relaxation. During normal development, the NM myosin is down regulated and smooth muscle (SM) myosin becomes the prevalent myosin isoform; however, in a person with CoA, this does not occur. The Brookfield East SMART (Students Modeling a Research Topic) Team has designed a model of SM myosin using 3D printing technology. The model focuses on the structure of dephosphorylated (unregulated) SM myosin S1 and S2 regions which interact with actin and generate contraction. The active sites for actin binding and ATP hydrolysis are on the S1 heads. Phosphorylation of myosin light chain 20 that associates with the S1 head regulates its function. When dephosphorylated, the two myosin heads bind to each other, blocking the actin binding sites, thereby preventing acto-myosin interaction and muscle contraction. While hypothesized to be involved in CoA, increased understanding of SM myosin may also help advance knowledge in other areas of SM research, possibly leading to cures for many other diseases including asthma and various digestive disorders.
Human Argonaute-2: For All Your RNA Slicing Needs

Brown Deer High School

Poster #5

Authors: Evan Bruss, T.J. Davis, Jack Hermsen, Justin Johnson, Robert Laughlin, Maurice Lucré, Chad Marable, Brett Poniewaz, Virginia Tuncel, Gina Wade, Michael Weeden

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School: Brown Deer High School

Mentor: Mark McNally, Ph.D., Medical College of Wisconsin, Microbiology and Molecular Genetics

Human cells have the remarkable capability to regulate protein production by degrading target mRNA by two pathways: RNA interference (RNAi) and micro RNA (miRNA). Central to these pathways is the protein Argonaute-2 (Ago-2). In the RNAi pathway, small RNAs derived from viruses are used by Ago-2 to slice virus mRNA, protecting the cells from infection. In the miRNA pathway, Ago-2 utilizes naturally occurring miRNA to slice cellular mRNAs to control protein production. Ago-2 works by binding small (~22 nucleotide) regulatory RNAs (siRNA and miRNA) to target mRNA by base pairing. Ago-2 attaches to the phosphate backbone of the regulatory RNA, that guides Ago-2 to the target RNA. The RNase domain of Ago-2 (containing His807, Asp669, Asp597, and Glu637 in its active site) then “slices” the target to initiate degradation. Scientists can reduce the level of disease-causing proteins (for example, in breast cancer) using the siRNA pathway. Determining the structure of Ago-2 allowed researchers to understand how this enzyme functions in the siRNA/miRNA pathways. The Brown Deer High School SMART (Students Modeling A Research Topic) Team has designed a model of Ago-2 using 3D printing technology to investigate its structure-function relationship. SMART Team programs are supported by a grant from NIH-CTSA.

Opioid Oppression Mu-Opioid Receptor (µOR)- a G Protein-Coupled Receptor (GPCR)

Wauwatosa West High School

Poster #22

Authors: Paige Bonner, Adam Fendos, Zaynab Hassan, Annalise Ho, Max Ho, Jeremy Kaine, Alec Lau, Simon Ng, Christopher Monty, Richard Sear, Aleksandra Zielonka

Teachers: Mary A. Haasch

School: Wauwatosa West High School

Mentor: Christopher Cunningham, Ph.D. Concordia University Wisconsin - School of Pharmacy

Opioid abuse is now a leading cause of accidental death in North America; yet, opioids remain the most prescribed drugs in the United States. Opioid drugs are powerful painkillers, but their adverse side effects — addiction, tolerance, and extreme constipation — severely limit their medical use. The mu-opioid receptor (µOR), is one of the G protein-coupled receptors (GPCR) traversing the cell membranes of primarily neuronal cells in the brain and spinal cord. µOR is embedded in the membrane of presynaptic cells in the brain. Normally, endorphins (such as beta-endorphins, which are classed as opiates) bind to the receptor, which results in a release of ions and a cascade to effector proteins (such as ion channels), ultimately leading to various reward circuit oriented behaviors and analgesic effects. Other opiates (natural derivatives, e.g. morphine), opioids (synthetic derivatives), and similar compounds instead bind to µOR, which prevents normal endorphin-binding activity. µOR is a single chain protein with 8 helices. Its active site is on the inside of the protein; binding involves 14 residues. Interactions between the other helices, disulfide bond (Cys140-Cys217), and salt bridge (Arg165-Asp164) stabilize the protein structure. Polar bonding between Thr279-Ile256 maintains the protein in the inactive state. Lys233 covalently binds to both morphine (agonist) and beta-FNA-funaltrexamine hydrochloride (antagonist). The Wauwatosa West SMART (Students Modeling a Research Topic) Team used 3D printing technology to study the structure/function relationship of the mu-opioid receptor. Currently, naltrindole partially excites the µ-active site without the loss of effectiveness overtime. Other chemicals need to be investigated that will provide an effective analgesic while eliminating all side effects.
Gonads Go Mad and the Effects of Neonatal Stress on Hypothalmic-Pituitary-Gonadal Function in Rats
Valders High School
Poster #21

Authors: Vanessa Bratz, Alyssa Christianson, Sanne De Bruijin, Elizabeth Evans, Meagan Green, Paige Howard, Supriya Leitner, Kristin Schneider, Mariah Ulness, Jacqueline Wenzel
Teachers: Joe Kinscher
School: Valders High School
Mentor: Karin Bondensteiner, Ph.D., University of Wisconsin Stevens Point, Professor of Biology

Neonatal stress may permanently alter hypothalamic-pituitary-gonadal function and accelerate the onset of puberty in female rats. Heterotrimeric G proteins, found coupled to membrane-bound receptors on the inside of cell membranes, form a central link in cell signaling. Inactive G proteins bind guanosine diphosphate (GDP). When a signaling molecule, such as gonadotropin releasing hormone (GnRH), binds to membrane receptors of cells in the anterior pituitary gland, GDP is displaced by GTP (guanosine triphosphate), and the alpha subunit separates from the beta and gamma subunits. The alpha-GTP subunit then triggers a cell signaling cascade. In pituitary gonadotroph cells, this cascade results in the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH). These hormones will cause female gonads (ovaries) to release estrogen and progesterone and, if hypothalamic-pituitary-gonadal function is altered, may trigger early onset of puberty in female rats. The Valders SMART Team modeled a G Protein using 3D printing technology to study structure-function relationships in cell signaling. Hydrophobic amino acids form the switch interface between the alpha subunit and the beta-gamma subunits stabilizing the heterotrimeric G protein. When the alpha subunit binds GTP, Gly199 interacts with the terminal (gamma) phosphate of GTP, and the activated alpha subunit separates from the beta-gamma subunits resulting in cell signal propagation. Understanding how the hypothalamic-pituitary-gonadal axis is influenced by neonatal stress in rats may help scientists to better understand puberty onset in humans.

The T Protein: Vertebrae Fit to a T
Cedarburg High School
Poster #6

Teachers: Karen Tiffany
School: Cedarburg High School
Mentor: Michael A. Pickart, Ph.D. Concordia University Wisconsin, School of Pharmacy

Congenital vertebral malformations (CVMs) comprise a group of spinal abnormalities that include alterations in vertebral shape or number. Evidence suggests CVMs have a genetic link, possibly resulting from mutations in multiple genes. One candidate gene is T. T protein, a transcription factor found in a variety of animals including humans, is essential for correct embryonic development and guides the development of bone and cartilage from embryonic mesodermal tissue. T protein accumulates in the nuclei of notochord cells, interacts with DNA at specific genes, and acts as a genetic switch to activate the genes. T protein binds to the major and minor grooves of DNA as a dimer. Mutations in T (turning “off” the T protein switch) are hypothesized to result in defects in spinal development. The Cedarburg SMART (Students Modeling A Research Topic) Team has designed a partial model of T protein using 3D printing technology to investigate its structure-function relationship, focusing primarily on the residues important for dimerization of T (Pro125, Asp126, and Pro128) and for binding DNA (Arg67). A 3D model could indicate how the location of the mutations may impact the function of T. T could consequently be a potential target for the development of treatment or prevention options. Program supported by a grant from NIH-CTSA.
Think Pink: The Role of Cytochrome Aromatase in Estrogen Production and Breast Cancer Risk P450
Cudahy High School
Poster #7

Authors: Samantha Brzezinski, Jason Hauk, Jose Bueno, Lauren Ligocki, Paige Broeckel, Katherine MacDonald, Kaylee Day, Cori Windsor, Emily Bahling, Cody Broeckel, Ramon Rivas, Kaycee Valine, Katya Tolbert
Teachers: Dan Koslakiewicz and Dean Billo
School: Cudahy High School
Mentor: Piotr Mak, Ph.D., James Kincaid, Ph.D., Marquette University, Department of Chemistry

According to the American Cancer Society (2012), postmenopausal women with high levels of endogenous hormones have about twice the risk of developing cancer compared to women with the lowest levels. A key protein for estrogen biosynthesis from androstenedione (AD), and possibly linked to development of breast cancer, is cytochrome P450 aromatase (CYP19A1) found in adipose breast tissue. CYP19A1 converts AD to an aromatic C18 estrone through two consecutive hydroxylations at the C19 methyl group and catalyzing a third lyase step, culminating in cleavage of the C10–C19 bond of the C19-aldehyde, with concurrent aromatization of the A ring of the steroid framework. AD is attracted to the active site by Arg192, Asp309, and Glu483. A heme group, bound in the CYP19A1 active site by Cys437, is responsible for these 3 oxidation steps. The key residues were modeled by the Cudahy SMART (Students Modeling A Research Topic) Team using 3D printing technology. The heme group binds molecular oxygen and then forms strong oxidizing intermediates that achieve these difficult oxidation reactions. The resonance Raman technique provides detailed structural insight into these important but unstable heme intermediates. Gaining an understanding of the reaction mechanism of CYP19A1 is important. If it can be learned how CYP19A1 functions, a suppression treatment to disable local estrogen production in breast adipose tissue by CYP19A1 could be developed by scientists to control estrogen levels, possibly reducing tumor growth or diminishing the risk of development of breast cancer.

Thrombin: Nature’s Band Aid
Saint Joan Antida High School
Poster #20

Authors: J.D. Allen, J.T. Allen, A. Alvarez, F. Garcia, S. Kopacz, A. Ray
Teachers: Emily Harrington Vruwink
School: Saint Joan Antida High School
Mentor: Dr. Anja Blecking, Ph.D. and Megan Josephine Corby, Ph.D.
Candidate University of Wisconsin-Milwaukee, Department of Chemistry & Biochemistry

Normal blood flow plays an essential role in many life processes. If an abrasion to the blood vessels disrupts normal blood flow. A protein called thrombin acts as a signaling cascade that forms a clot and fixes the abrasion. Thrombin is the central molecule in hemostasis, which is the process of stopping blood flow. When blood vessels are cut open, Factor VII – a protein that helps the process of blood clotting – is released and comes into contact with tissue factor found on cells. When this happens, factors V, IX, and X are activate. Collectively, these factors trigger the signaling cascade that results in the activation of thrombin. Thrombin is circulated in plasma as prothrombin, which is the inactive state of thrombin. Thrombin catalyzes the conversion of fibrinogen into fibrin, which then constructs an insoluble network of fibers that eventually dries to form a scab. The Saint Joan Antida SMART (Students Modeling a Research Topic) Team has modeled thrombin using 3D printing technology. Thrombin is a serine protease composed of two chains. The active site amino acids involved in cleaving the peptide bonds in fibrinogen are His-57, Asp-102, and Ser-195. Defective thrombin can either lead to too few or too many blood clots. Too little clotting could result in a disorder called hemophilia; too much could result in deep vein thrombosis (DVT) – a blood clot in major leg veins. DVT could lead to less blood flow to the heart, causing a stroke or heart attack. Research continues on the role thrombin plans in the progression of hemostasis and restoring the balance of homeostasis.
Hepcidin: The Key Regulator of Iron in the Blood
Saint Dominic School
Poster #17

Authors: Eclaire Jessup, Dominic Kowalik, Claire Lois, Alyssa Larcheid, Samuel Larcheid, Sara Maslowski, Emma Pittman, Joseph Platz, Marissa Puccetti, Tyler Shecterle, Nicole Simson, Emma Wenger
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School: Saint Dominic
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Hepcidin, a peptide hormone, is the key regulator of plasma iron levels in humans, and is known to play an important role in various human diseases, such as hemochromatosis. Hepcidin inhibits the entry of iron into circulation by binding to ferroportin, a trans-membrane iron export channel found primarily on enterocytes, hepatocytes and macrophages where iron is sequestered. When hepcidin binds to ferroportin, both are drawn into the cell by endocytosis and degraded in a lysosome. When hepcidin levels increase, ferroportin levels on cells decrease and iron cannot be released from cells into the blood. Hepcidin production by the liver is affected by erythropoiesis in bone marrow, blood oxygenation, certain inflammatory cytokines, intracellular iron storage, and plasma transferrin. The St. Dominic SMART Team (Students Modeling A Research Topic) has modeled hepcidin using 3D printing technology. Hepcidin is a 25 amino acid, β hairpin containing one beta sheet, and four disulfide bonds (Cys1-Cys8, Cys3-Cys6, Cys2-Cys4, and Cys5-Cys7). Removal of the first five amino acids of hepcidin strongly decreases its ability to bind ferroportin and trigger endocytosis. Tests are currently commercially available for measuring both urine and plasma hepcidin concentrations, and research into their clinical applications is underway. Hepcidin is not currently being used to treat iron disorders, but hepcidin agonists and antagonists are being developed and investigated for possible future therapeutic use.

Modeling TRPV1, a Detector of Thermal and Chemical Stimuli, Producing Pain: No Capsaicin Sensation
Divine Savior Holy Angels High School
Poster #8

Teachers: Stacey Strandberg and Scott Fleischmann
School: Divine Savior Holy Angels High Savior
Mentor: Andy Weyer, DPT, Ph.D. Candidate & Katherine Zappia, Ph.D. Candidate, Medical College of Wisconsin, Department of Cell Biology, Neurobiology and Anatomy

According to the Institute of Medicine, 100 million Americans suffer from chronic pain every year and the US spends over $500 billion trying to treat them. Pain begins as a stimulus that is detected by nociceptors, which are nerve fibers responsible for the detection of noxious mechanical, thermal, or chemical stimuli that give rise to pain sensations. These nociceptors transmit pain signals from the periphery to neurons in the spinal cord and brain. The Transient Receptor Potential Vanilloid 1 (TRPV1) is a nociceptive ion channel activated by capsaicin (the spicy component of hot peppers), heat, and endogenous pain molecules. Therefore, creating an inhibitor that partially blocks TRPV1 could treat chronic pain. The amino acids in the active site of TRPV1 are Y511, S512, M547, and T550. In addition, E600 controls the selectivity filter at the top gate of the channel and the hydrophobic seal mediated through I679 controls the lower gate. When capsaicin binds to the channel, a conformational change occurs that pulls the I679s on each subunit away from each other, opening up the lower gate. Understanding how activation of TRPV1 occurs may lead to the discovery of novel inhibitors of TRPV1 to help treat those suffering from chronic pain and reduce healthcare spending. The Divine Savior Holy Angels SMART (Students Modeling A Research Topic) Team modeled TRPV1 in a partially activated state using 3D printing technology. Program supported by a grant from NIH-CTSA.
CI-MPR: The Lysosomal Enzyme Receiving Superstar  
Grafton High School  
Poster #9

Authors: Robyn Ahrenhoerster, Amber Amendza, Eli Bolker, Brittany Cassel, Chloe Lichosik, Rebecca Milliken, Andrew Mosin, Nick Pavelic, Ashleigh Perry, Hannah Weber, Sara Zimmerman

Teachers: Dan Goetz, Fran Grant

School: Grafton High School

Mentor: James Miller, MD/PhD Candidate Medical College of Wisconsin, Department of Biochemistry

Fabry disease is X-linked and occurs from a deficiency of α-galactosidase A, a lysosomal enzyme that normally degrades the ganglioside globotriaosylceramide (Gb3). Lysosomal accumulation of Gb3 results in cardiovascular, renal, and neurological pathologies, and hemizygous males with Fabry disease tend to have the most severe presentations. The cation-independent mannose 6-phosphate receptor (CI-MPR) recognizes lysosomal enzymes bearing a mannose 6-phosphate (M6P) tag via the amino acids Gln644, Arg687, Glu709, and Tyr714 in its fifth domain, and transports these enzymes from the trans-Golgi network to the lysosome. Four out of CI-MPR’s 15 domains are able to bind M6P or M6P conjugated to N-acetylglucosamine. CI-MPR is also present at the cell surface, and this localization can be exploited to deliver exogenous M6P-tagged biomolecules (i.e., α-galactosidase A) to the lysosome. Intravenous enzyme replacement therapy (ERT) for Fabry disease is extremely expensive, inefficient, and immunogenic. Determining the 3-D structure of CI-MPR is crucial in improving the efficiency of Fabry ERT because this knowledge will allow for the rational design of recombinant α-galactosidase A with optimally placed M6P moieties. The Grafton SMART (Students Modeling A Research Topic) Team will create a physical model of CI-MPR domain 5 using 3-D printing technology, which is made possible by a grant from NIH-CTSA. Further structural studies of CI-MPR will not only lead to a reduction in ERT cost, but will also improve the lives of those suffering from Fabry disease.

RecQ DNA Helicases in Human Disease  
Monona Grove High School  
Poster #18

Authors: Bradley Hanson

Teachers: Sarah Wright

School: Monona Grove High School

Mentor: James Keck, PhD, Department of BioMolecular Chemistry, University of Wisconsin School of Medicine and Public Health, Madison, WI

Many cellular processes are regulated and maintained through genetic recombination. RecQ DNA helicases form a very important family of enzymes that drives this activity in cells. Recombination is initiated by RecQ unwinding paired double-stranded DNA using ATP hydrolysis as the chemical fuel during this process. In addition to recombination, RecQ helicases also have ties to cellular aging, gene silencing, and DNA repair, and organisms that lack RecQ due to mutations are plagued by genomic instability and a predisposition to cancer. Three heritable human diseases have been linked to mutations in genes that encode RecQ helicases. Mutations in these genes, WRN gene in Werner Syndrome, BLM gene in Bloom's Syndrome, and RECQ4 in Rothmund-Thomson Syndrome, can give the rise to diseases of premature aging, cancer, type 2 diabetes, osteoporosis and atherosclerosis. Over the past decade, a considerable amount of research has focused on the cellular functions, genomic regulation, and maintenance of RecQ helicases. Our study has focused on high-resolution X-ray crystal structures of the core region shared among RecQ helicases and on how mutations within this domain could be linked to human diseases. We also discuss how researchers think that RecQ helicases cooperate with another enzyme, topoisomerase, to function in genomic maintenance.
Whoop There It Is: The Role of Pertussis Toxin in Symptom Longevity
Milwaukee Academy of Science
Poster #17

Authors: LaTyra Barnes, Brandi Duadon, Santana Johnson, VirginiaRose McCotry, Thyvin Nash, Jason Roby, Reauna Taylor, Quintien Tyra David Washington, and Joshua Washington
Teachers: Kevin Paprocki and Tyler Reed
School: Milwaukee Academy of Science
Mentor: Joseph Barbieri, Ph.D. and Faith Blum, Ph.D.
Medical College of Wisconsin, Department of Microbiology and Molecular Genetics

AIDS and Ebola are seen as some of the most frightening diseases on the planet; however, a more infectious disease is on the rise. Pertussis, known as whooping cough, has over a 90% transmission rate between members of the same household. More frightening than its virulence and preventability is its role in infant mortality. Pertussis is a respiratory disease that causes a violently uncontrollable cough and breathing difficulty. Even with immunization, over 48.5 million infections occurred in 2012, with infants accounting for 83% of deaths. Pertussis is caused by a species of bacteria called Bordetella pertussis (Bp), which is an airborne, aerobic coccobacillus pathogenic only to humans. Bp infects humans by colonizing respiratory epithelium and producing tracheal cytotoxin, which prevents the cilia from clearing debris from the respiratory tract. Bp then produces pertussis toxin (PT), which binds to a cell-membrane receptor. The Milwaukee Academy of Science SMART (Students Modeling A Research Topic) Team modeled the pertussis toxin using 3D printing technology. PT is an AB5 toxin, and exhibits ADP-ribosyltransferase activity. The toxin is endocytosed into respiratory epithelium and traffics through the endocytic pathway through the Golgi complex into the endoplasmic reticulum. The S1 subunit translocates into the cytosol, where the S1 subunit ADP-ribosylates a Gai protein. This prevents normal migration of leukocytes to the site of infection. This leukocyte immobility contributes to the longevity of symptoms and overall lethality. A greater understanding of this toxin will inevitably result in a more effective and enduring vaccination protocol than currently implemented.

Hungry Like PACAP Man- Role of PACAP and PACAP-36 in Eating Behaviors
Greenfield High School
Poster #10

Authors: J Wallner, T Shaik, P Emkay, K Kelly, K Cavins, F Deleon-Camacho, D Alphin, A Braatz, E Groth, J Piotrowski, L Granlund, V Krenz
Teachers: Julie Fangmann and Drew Rochon
School: Greenfield High School
Mentor: SuJean Choi, PhD, Marquette University

According to the CDC, 34.9% of United States adults are obese, which is linked to premature death, heart disease, cancer, respiratory disorders, fertility problems, Type 2 diabetes, and stroke. Over- and under-eating are related to brain chemistry. A 38 amino acid peptide hormone in the hypothalamus, called pituitary adenylate cyclase-activating peptide (PACAP), may be linked to eating disorders. PACAP binds to PACAP type 1 receptor (PAC1R), a G-protein coupled receptor. Seven hydrophobic transmembrane (TM) domains hold PAC1R in hypothalamic cell membranes. PAC1R’s extracellular domain (ECD) contains a ligand binding site. PAC1R’s many negative residues attract PACAP’s many positive ECD residues. PACAP’s V19, K20, and L27 affect PACAP binding to PAC1R. K20 forms a possible salt bridge with PAC1R’s G104, allowing PACAP to align parallel to PAC1R so PACAP’s N-terminus interacts with PAC1R’s TM domains. This activates PAC1R, sending a signal inside the cell. Too much PACAP may cause a person to stop eating and lead to eating disorders. PACAP6-38 is an antagonist formed when a protease removes the first five PACAP residues. When PACAP6 -38 binds to PAC1R, eating increases, possibly leading to obesity. SuJean Choi, PhD wants to determine how ratios of PACAP and PACAP6-38 are regulated. The Greenfield SMART (Students Modeling A Research Topic) Team modeled PAC1R’s ECD and its two ligands, PACAP and PACAP6-38, using 3D printing technology to investigate their relationships. Studying PACAP and PACAP6-38 regulation and brain chemistry involved in eating behaviors could improve people’s lives and decrease obesity-related US medical costs. Program supported by a grant from NIH-CTSA.
Not So Hot Rods: Mutations in Rhodopsin Kinase in Regards to Oguchi Disease
Hartford Union High School
Poster #11

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School: Hartford Union High School
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The average person's eyes adapt to darkness within minutes. For those with Oguchi's disease, adaptation can be slowed to several hours. Oguchi disease is an autosomal recessive disorder that results in greatly slowed phototransduction. Phototransduction is a cascade reaction beginning with a photon activating rhodopsin in the rod and leading to hyperpolarization of the cell. Oguchi disease is caused by mutations in rhodopsin kinase which prevent the phosphorylation of rhodopsin, lowering rhodopsin's affinity for arrestin. This reduced ability to bind arrestin decreases the speed in which rhodopsin is deactivated and prepped to reactivate. After a long period in a dark environment, the rhodopsin is eventually deactivated by arrestin, allowing it to be recycled. The Hartford Union High School SMART (Students Modelling a Research Topic) Team has designed a model of rhodopsin kinase to investigate its structure-function relationship. Oguchi disease can be caused by two different mutations in rhodopsin kinase: large deletion or point mutation. In our 3D model, we will highlight the complete deletion of exon five, the partial deletion at the C-terminus, and point mutations in the catalytic domain (Val380Asp and Pro391His) that cause Oguchi disease. Understanding the structure-function relationships of rhodopsin kinase could shed more light on night blindness. This program is supported by a grant from NIH and CTSA.

Allosteric Modulation of CB₁ by Pregnenolone
Messmer Catholic High School
Poster #16

Authors: Alex Camacho, Brigitte Rios, Tariq McKinney
Teachers: Justin Spaeth
School: Messmer Catholic High School
Mentor: Aaron Miller, Ph.D. Assistant Professor of Physiology at Concordia University

The endocannabinoid system plays a role in diverse conditions such as anxiety, addiction, eating and memory disorders. Endocannabinoids are produced by postsynaptic neurons and activate receptors on presynaptic neurons in order to decrease neurotransmitter release. In the brain, the most important receptor activated by endocannabinoids is cannabinoid receptor type 1 (CB₁). Tetrahydrocannabinol (THC), the active ingredient in marijuana, also activates this receptor. THC and similar drugs have therapeutic potential in the treatment of pain, Alzheimer's disease, anxiety, arthritis, and cancer. A downside to the medicinal use of THC is that it also induces psychotropic effects. Recently, it was discovered that pregnenolone binds to CB₁, where it acts as an allosteric modulator that decreases the effects of THC. An allosteric modulator is a molecule that modifies receptor function by binding somewhere other than the active site. Discovery of allosteric modulators is significant because it means that there may be additional ways to target CB₁ that have a reduced rate of psychotropic effects. The Messmer SMART (Students Modeling a Research Topic) Team has created a model of CB₁ bound to pregnenolone using 3D printing technology. Our model highlights the amino acids E133 and R409, which form hydrogen bonds with pregnenolone and are required for its binding to the allosteric site of CB₁. Studying the interaction between CB₁ and pregnenolone will allow for a greater understanding of the interaction between synaptic function and pregnenolone levels as well as the design of additional allosteric modulators for testing as therapeutics. This program is supported by a grant from NIH-CTSA.
Nicotinamide Phosphoribosyltransferase (NAMPT) Inhibition Yields Promising Future Implications Marquette University High School Poster #15

Authors: T Sabatino, J Tsuji, N Yorke, R Johnson, K Arnhold, J Otten, P Ahn, K Cephus, A Dittlof, L Ortega, H Foster, M Hernandez, M Rivera, D Strom, J Strom, N Yang, N Dittrich
Teachers: Mr. Carl Kaiser and Mr. Keith Klestinski
School: Marquette University High School
Mentor: Mr. Matthew Waas, Ph.D. Candidate, Medical College of Wisconsin.

Human embryonic stems cells (hESC) and induced pluripotent stem cells (hiPSC), collectively termed human pluripotent stem cells (hPSC), differentiate into any cell type. The creation of hPSC free from potentially tumorigenic pluripotent stems is advantageous for research strategies and necessary for future hPSC-based clinical therapies. The STF-31 molecule inhibits an important metabolic enzyme, NAMPT, providing selective toxicity of hPSC in diverse cell culture conditions. This strategy effectively eliminates potentially tumorigenic cells but spares differentiated progeny. The MUHS SMART (Students Modeling A Research Topic) Team has designed a model of NAMPT bound with STF-31 using 3D printing technology. What makes STF-31 unique as a NAMPT inhibitor is its ability to occupy the protein's active site and act as a substrate for the enzyme. The pyridine ring of STF-31 is situated between the F193 and Y188 sidechains of NAMPT. The central phenyl ring of STF-31 occupies the tunnel region of NAMPT. Other binding sites between STF-31 and NAMPT include H191, R196, S241, V242, A244, S275, I309, and R311. NAMPT inhibition research will lead towards the development of clinically safe hPSC progeny for human stem cell based therapies, drug development, and toxicity testing. This is supported by a grant from NIH-CTSA.

N-methyl-D-aspartate (NMDA) Receptor Kettle Moraine High School Poster #12

Authors: Mahi Gokuli, Jerad Grewe, Ethan Helfenstein, Lindsay Jost, Samuel Kanakkanatt, Rylie Morris, Christina Nielsen, Justin Smet, and Andrew Straka
Teachers: Melissa Kirby
School: Kettle Moraine High School
Mentor: Robert W. Peoples, Ph.D., Marquette University, Department of Biomedical Sciences

Alcohol affects our world more than any other drug. As the third leading preventable cause of death, it is adolescents’ drug of choice, and parental alcoholism impacts the lives of one in four children. Alcohol consumption interferes with communication between neurons in the central nervous system, causing symptoms such as motor incoordination and memory impairment. The NMDA receptor, an ion channel located within neuronal membranes, is a major target upon which alcohol acts. When activated by the signaling molecule glutamate, a gate in its membrane-associated (M) domains opens; allowing calcium and sodium cations to enter the neuron through its ion channel. Alcohol, however, interferes with this process by binding to the M domains, preventing cations from entering the neuron and causing many of the known effects of alcohol consumption. Mutations at positions in the M domains, such as M823 in the GluN2A M4 domain and F636 in the GluN2A M3 domain, have been found to significantly alter alcohol sensitivity; making it less susceptible. The Kettle Moraine High School's SMART (Students Modeling A Research Topic) Team has designed a model of the NMDA receptor using 3D printing technology to investigate structure-function relationships. Further research on the interactions between alcohol and the NMDA receptor could aid in finding a solution to the abuse of this historically documented and often detrimental drug.
[FeFe] Hydrogenase in Artificial Photosynthesis
Laconia High School
Poster #13

Authors: Noah Henke, Alex Wood, Carissa Zibolsky, Allison Opheim, Ashley Garb
Teachers: Jodie Garb
School: Laconia High School
Mentor: Jier Huang, Ph. D., Marquette University

The development of clean and renewable energy is critical to partially address the energy crisis and climate issues. Inspired by nature, artificial photosynthesis through water splitting by solar energy conversion is the most attractive approach for the development. The overall water splitting includes two half-catalytic reactions, i.e. hydrogen (HER) and oxygen (OER) evolution reactions. An efficient catalyst is required to perform each of these catalytic reactions. Molecular catalysts that mimic the function of [FeFe] hydrogenase are among the most effective synthetic transition metal complexes known for HER. The Laconia SMART (Students Modeling A Research Topic) Team used 3D printing technology to model the active site of [FeFe] hydrogenase and understand its catalytic function for HER. [FeFe] hydrogenase is an enzyme that catalyzes proton reduction to bind hydrogen together. Arg265, Lys288, and Lys409 are positively charged residues that line the channel entrance. Lys 188 is at the end of the channel and may help to orient the 2Fe subcluster during hydrogen insertion. The fundamental understanding of the catalytic function of the [FeFe] hydrogenase active site in HER will provide insight into the rational design of efficient catalysts for solar fuel generation. The SMART Team program is supported by a grant from NIH-CTSA.

Understanding the µ-Opioid Receptor Protein Binding Site Interactions with Ligands
Madison West High School
Poster #14

Authors: Yuanqi Cai, Jacob May, Helen Deng, Thomas Luo, Charles Hua
Teachers: Tricia Windgassen and Christine Petzold
School: Madison West High School
Mentor: Chris Cunningham, Ph.D, School of Pharmacy, Concordia University, Wisconsin

Opium and its derivatives have been used for centuries to treat severe acute or chronic pain by binding to opioid receptors in the body, causing beneficial effects of analgesic and harmful effects. Their addictiveness has led to several opiates becoming recreational drugs such as opium, morphine, and oxycodone. In addition, people build up tolerance to opiates decreasing their effectiveness over time. The main opioid receptors, µ-opioid receptors (µ-OR), are G-protein coupled receptors (GPCRs) that undergo conformational changes when a ligand such as opium or morphine binds to it, initiating a downstream effect that ultimately relieves pain. If scientists can understand the molecular interactions when drugs bind these receptors, they can begin to develop a drug that binds these receptors to relieve pain without signaling these negative side-effects. The crystal structure of the µ-opioid receptor bound to a morphinan antagonist reveals an unusually large binding pocket, allowing quick binding and many different molecules to bind with it. Residues around the binding site contact the bound molecule differently depending on the molecule. It is believed the triggering of these residues is what affects the person. The Madison West High School SMART (Students Modeling a Research Topic) Team modeled this bound G-protein coupled µ-OR by using Jmol protein modeling software and 3D printing technology to investigate the structure and function relationships of receptor interactions. An understanding of the binding site interactions of µ-OR, along with other structures that capture the active form of this bound receptor, will help researchers start to develop more useful drugs.