The MSOE Center for BioMolecular Modeling would like to acknowledge and thank the National Institutes of Health Science Education Partnership Award (NIH-SEPA 1R25OD010505-01) and the National Institutes of Health Clinical and Translational Science Award (NIH-CTSA UL1TR001436) for their support in funding the 2016-2017 SMART Team program.

Chlorotoxin
based on 1chl.pdb

Life is Complicated ...
Let’s deal with it!
The Local Mentor-Matched SMART Team Program

The Local Mentor-Matched SMART Team Program introduces students and their teachers into the “community of science” through partnering with a scientist to explore a research topic in depth. The local program consists of three phases: the Qualification Phase, the Research and Model Design Phase, and the Presentation Phase. During the Qualification Phase, MSOE staff direct the students to complete a series of tasks under the guidance of their teachers to demonstrate their knowledge of the basics of protein structure/function and computer visualization of biomolecules. Upon successful completion of the qualification exam, each team enters into the Research and Model Design Phase where they are paired with a research scientist mentor. The students work with their mentor to investigate a selected aspect of the mentor’s research topic by reading primary citations, visiting their mentor’s lab, writing an abstract and designing a molecular model. A poster session during the Presentation Phase provides the students with an authentic experience to communicate their molecular story through the poster and 3D model they have designed. These presentations encourage the SMART Team students to develop their communication skills – skills that will benefit them regardless of their future career paths.

Local Mentor-Matched SMART Teams and Advisors

Audubon High School
Brown Deer High School
Cedarburg High School
Cudahy High School
Divine Savior Holy Angels
Grafton High School
Hartford Union High School
Kettle Moraine High School
Marquette University High School
Saint Joan Antida High School
Saint Dominic School
Westosha Central High School
Whitefish Bay High School

Brian Coffey & Julissa Chavez
David Sampe
Karen Tiffany
Dan Koslakiewicz & Dean Billo
Stacey Strandberg & Scott Fleischmann
Fran Grant
Mark Arnholt
Melissa Kirby
Carl Kaiser & Keith Klestinski
C. McLinn, A. Montgomery, K. DiFonzo
Donna LaFlamme
Jonathan Kao
Paula Krukar & Katie Brown
National SMART Team Program

In the National SMART (Students Modeling a Research Topic) Team program, teams of students and their teachers from across the country delve into the molecular world, explore science as a process and work closely with a scientist mentor from a research institution near their school. Together they explore and learn the structure-function relationship of a specific protein in relation to the research being done in the mentor’s laboratory. They then design a model of the protein of interest that highlights important structural features that allow them to present their molecular story using a physical representation of the protein that they developed.

The National SMART Team program is available to schools across the US and Canada. This school year, we have 28 teams participating the the National SMART Team program. In addition to this MSOE event, we have teams who will present at the Experimental Biology conference in Chicago next month, and others will present in NYC in May.

National SMART Teams

Brookfield East High School
The Independent School
Madison West High School
Monona Grove High School
Valders High School

Presentations

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Calbindin: A Marker for Synaptic Integration Following Spinal Injury

Audubon High School
Poster #1

Authors: Sumaya Ahmed, Roberto Arce, Jehousa Gomez-Mendez, Rolando Martinez
Teachers: Julissa Chavez and Brian Coffey
Mentor: Audra Kramer, MS
Marquette University, Department of Biomedical Sciences

The World Health Organization reports that 250,000 to 500,000 people suffer a spinal cord injury annually. The injury interferes with presynaptic to postsynaptic communication necessary for proper motor function. Neurons do not typically regenerate, rendering damage permanent. To work around this damage, a virus that expresses an axon growth-promoting protein is injected into the motor cortex. This induces regeneration of injured axons and synaptogenesis. However, newly sprouted axon-to-cell connections can be mistargeted. The integration of newly regenerated axons with postsynaptic cells can be seen by studying the expression of postsynaptic cell markers, such as the calcium-binding protein calbindin. Calbindin contains twelve alpha helices, four calcium binding sites, and six EF-hands. Calbindin connects EF-hands by making hydrophobic contacts to amino acids on each arm. Ile19, trp20, and phe23 from the first arm make contact with leu36, leu39, and ala46 on the second hand while an EF-hand loop is made by contacts between asp24 and ala46. The two cystine residues, cys100 and cys219 play an important role in calcium binding in the protein. Calbindin is more heavily expressed in classes of cells found in the ventral portion of the spinal cord, suggesting a role in motor function. The Audubon High School SMART (Students Modeling a Research Topic) Team has designed a model of calbindin using 3-D printing technology to investigate structure-function relationships. Using calbindin as a marker to identify the location of synaptogenesis in regenerating axons can lead to therapies for regaining motor function in individuals suffering from spinal cord injuries.

MAPS Team Program

Modeling A Protein Story (MAPS) is a relatively new CBM student program in its 2nd year that allows teams of students and teachers to model the unique structure-function relationships of a specific protein and then explore and develop a related protein story. The selected protein family for the 2016-17 school year was globins. Teams have utilized online resources and hands-on models to investigate the unique structure-function relationships of the oxygen-binding proteins that maintain the evolutionarily conserved structure, the “globin fold”. Teams then “map” out a path to explore through which they will gain a better understanding of how specific globins function, the difference between the structure-function of monomeric globins and tetrameric hemoglobin, as well as exploring how specific mutations result in dysfunction and disease.

The MAPS Team program is available to schools across the US and Canada. This school year, 32 teams had a MAPS team dedicated to modeling our featured protein. In addition to this MSOE event, we have teams who will present at the Experimental Biology conference in Chicago next month, and others will present in NYC in May.

MAPS Teams

Brookfield Central High School
Greenfield High School
Waukesha STEM School
Wisconsin Virtual Learning
Between 1820 and 1970, several members of the Fugate family in Kentucky were born with blue-tinged skin and mild neuropathy. This was due to type-II methemoglobinemia, a recessively inherited disease that causes excessive methemoglobin buildup in the blood. This hinders gas exchange, because methemoglobin (metHb) has a problematically high oxygen affinity, making it difficult for oxygen to be released to the cells. Usually, the enzyme cytochrome b5 reductase converts metHb to hemoglobin (Hb) via the flavin adenine dinucleotide (FAD) cofactor, which facilitates the reduction of metHb ferric ions to Hb ferrous ions. In type-II methemoglobinemia, however, the reductase is deformed. There are over 65 methemoglobinemia-causing mutations in the CYB5R3 gene, which codes for cytochrome b5 reductase. The Brookfield Central MSOE Center for BioMolecular Modeling MAPS Team used 3D modeling and printing technology to examine three particular methemoglobinemia-causing mutations of cytochrome b5 reductase. First, mutations in valine 90 and serine 145 create an incorrect isomer configuration, resulting in an unstable protein structure. Second, when cysteine 273 and cysteine 283 are altered, FAD is unable to facilitate the reduction properly. Finally, deletion of phenylalanine 298 renders the enzyme incapable of catalyzing the reaction that converts metHb to Hb. Investigating these mutations could assist scientists in determining diagnosis methods and treatment programs, as well as in discovering how the condition arose in the Fugate family in the first place.
The rising threat of nuclear terrorism necessitates proactive research to mitigate injury by radiation. Since one of the most damaging effects of radiation is the reduction of small blood vessels in healthy tissue, radiation-induced organ damage may be lessened by increasing blood vessel density. The Notch-Dll4 pathway plays an integral role in the development of blood vessels (angiogenesis). More recently, it has been reported to modulate mammalian vessel regression by initiating vessel occlusion that ultimately leads to vessel death. Expressed on endothelial cells lining blood vessels and on certain bone-marrow derived cells, Delta-like ligand 4 (Dll4) is a Notch-receptor ligand. Ser28, Leu107 and Pro206 are all critical amino acids in ligand interaction between Notch and Dll4. Dll4 regulates vascular development by modulating tip and stalk cells in maturing vessels. Moreover, genetic and pharmacological inhibition of Dll4/Notch prevents capillary regression in a model of retinopathy. These results suggest that Dll4 inhibition may reduce the development of many diseases stemming from vascular insufficiency including radiation injuries. The Brookfield East High School SMART (Students Modeling A Research Topic) Team has designed a model of Dll4 using 3D printing technology to investigate structure-function relationships. Radiation is used clinically to treat cancer but healthy tissue surrounding a tumor invariably receives damaging doses. By understanding the role of Dll4 in vascular regression, excessive damage to normal tissues can be avoided during radiotherapy or from a nuclear accident or attack.
The SMARTquelle Structural Biology Program is a free fall semester program offered through Marquette University that promotes structural biology education through direct, hands-on experience with protein structure determination for local high school students. The purpose of the program is to provide a diverse group of high school students an opportunity to experience the process of research in an engaging and challenging environment. Lab participants expressed four fluorescent proteins (mPlum, GFP, mCherry, and Citrine) in bacteria and purified these proteins to subsequently determine the protein structure by X-ray crystallography. These proteins were chosen because of their unique fluorescent properties and it allowed the students to visualize the protein through the various stages of protein purification and protein crystallization. Fluorescent proteins are also great models to use to understand how protein structure relates to function. Each group of students were given an unknown fluorescent protein at the beginning of the semester. To determine which protein belonged to each individual group, there were seven main experiments performed including: transformation, cell growth and induction, protein purification, screening conditions for crystallization, crystal refinements, and X-ray diffraction. The students were able to purify and characterize their fluorescent proteins based on observations made throughout the research experience. Even though they were unable to diffract their protein crystals, they practiced the essential skills necessary for protein crystallization and X-ray diffraction. As stated by the students, “Ultimately, the SMARTquelle program propagated not only the understanding of biochemistry among young scientists, but also the passion to explore the world through the lens of science”. We are now accepting applications for the 2017 program for interested high school students.

Authors: Harsimra Kalsi, Lija Wang, Abigail Arnholt, Pratyusha Emkay, Melody Ly, Mahi Gokuli, Autumn Saunders, and Katerina Tadlock
Program Instructor: Brittney N. Wyatt
Program Director: Martin St. Maurice
Marquette University, Department of Biological Sciences

According to the U.S. Centers for Disease Control and Prevention, each year 88,000 people die from alcohol-related causes in the United States. Ethanol misuse, a deadly and expensive societal problem, cost the United States $249 billion in 2010 (1). Ethanol targets many proteins in the brain. Specifically, it acts as an inhibitor of the N-Methyl-D-aspartate receptor (NMDAR), which mediates much of the excitatory synaptic transmission in the brain. Normally, the NMDAR is activated when glutamic acid binds to it allowing positive ions to flow through the cell membrane; this facilitates learning and memory in the brain. However, ethanol inhibits the activity of the NMDAR, interfering with synaptic transmission. A type of glutamate ion channel receptor found in neurons, NMDAR, has four domains: the amino terminal domain, the ligand binding domain, the membrane-associated (M) domains, and the carboxy terminal domain. NMDAR is a heterotetrameric protein with two GluN1 and two GluN2 subunits. Ethanol interacts with NMDAR in the M domains with specific amino acids including Gly638 in the GluN1 subunit as well as Phe637 and Gly826 in the GluN2B subunit (2,3). Researchers are determining the location of the strongest NMDAR-ethanol interactions using amino acid substitutions. The Brown Deer High School SMART (Students Modeling A Research Topic) Team has designed a model of NMDAR using 3D printing technology to visualize the NMDAR-ethanol interactions. If researchers can develop molecules to help minimize the effect of ethanol on the brain, it could reduce the cost of alcoholism to society.

Authors: Gavin Block, T.J. Davis, Nancy Dong, Jonah Freuler, Mitchell Mietkowski, Toni Jo Rowney, Noel Stoehr
Teacher: David Sampe
Mentor: Robert Peoples, PhD
Marquette University

According to the U.S. Centers for Disease Control and Prevention, each year 88,000 people die from alcohol-related causes in the United States. Ethanol misuse, a deadly and expensive societal problem, cost the United States $249 billion in 2010 (1). Ethanol targets many proteins in the brain. Specifically, it acts as an inhibitor of the N-Methyl-D-aspartate receptor (NMDAR), which mediates much of the excitatory synaptic transmission in the brain. Normally, the NMDAR is activated when glutamic acid binds to it allowing positive ions to flow through the cell membrane; this facilitates learning and memory in the brain. However, ethanol inhibits the activity of the NMDAR, interfering with synaptic transmission. A type of glutamate ion channel receptor found in neurons, NMDAR, has four domains: the amino terminal domain, the ligand binding domain, the membrane-associated (M) domains, and the carboxy terminal domain. NMDAR is a heterotetrameric protein with two GluN1 and two GluN2 subunits. Ethanol interacts with NMDAR in the M domains with specific amino acids including Gly638 in the GluN1 subunit as well as Phe637 and Gly826 in the GluN2B subunit (2,3). Researchers are determining the location of the strongest NMDAR-ethanol interactions using amino acid substitutions. The Brown Deer High School SMART (Students Modeling A Research Topic) Team has designed a model of NMDAR using 3D printing technology to visualize the NMDAR-ethanol interactions. If researchers can develop molecules to help minimize the effect of ethanol on the brain, it could reduce the cost of alcoholism to society.
Imagine life-threatening problems that appear when the brain doesn't have enough oxygen to function. Problems such as hypoxic/ischemic injury, leading to organ failure and tissue damage, arise when neuroglobin (Ngb) is insufficient in the brain. Neuroglobin is an oxygen binding globin protein and assists in augmenting oxygen supply to neural tissues in the Central Nervous System and Peripheral Nervous System. It is found predominantly in the retina, vertebrate, and brain. Neurons that make more than the average amount of neuroglobin are more resistant to oxygen deprivation. Therefore, neuroglobin is a factor in protecting the body against hypoxia, yet how the protein utilizes its protective effect remains unclear. Ngb's structure consists of alpha helices and four heme groups. In its hexacoordinated form, human neuroglobin displays a classical globin fold adapted to host the reversible bis-histidyl heme complex and an elongated protein matrix cavity, held to facilitate oxygen diffusion to the heme (displacement of the HisE7 heme ligand leads to Ngb oxygenation). In recent scientific studies, Ngb has been proven to assist in the protection of neurons from mitochondrial dysfunctions, neurodegenerative disorders (such as Alzheimer's), and cancer cells. The MAPS Team used 3D printing to model the Ngb protein, primarily highlighting amino acids leu27, phe28, leu31, phe42, tyr44, his64, lys67, val68, val109, ile72, leu92, his96, phe106, val109, leu113, trp133, leu136, tyr137, and val140. The function of Ngb is uncertain, making further research imperative to the future of neurological disorders and their treatment.
Opioid addiction and abuse affects between 26 and 36 million people worldwide (Volkhow, 2014), prompting researchers to try to design a drug that both has painkilling effects but does not create a dependency. Most opioid analgesics work through activation of mu opioid receptors (MOR). They naturally bind to opioid peptides, such as endomorphins 1 and 2, in order to regulate pain. Another important target is the delta opioid receptor (DOR). Inhibition of DOR has been shown to slow the development of addiction to MOR agonists in animal models of pain. DOR are proteins that transpermeate the cell membrane with seven alpha helices. Schiller and colleagues first reported an endomorphin analogue, DIPP-NH2, that activates MOR and also inhibits DOR. DIPP-NH2 has been shown to slow the development of addiction to MOR agonists in animal models of pain. DOR are proteins that transpermeate the cell membrane with seven alpha helices. Schiller and colleagues first reported an endomorphin analogue, DIPP-NH2, that activates MOR and also inhibits DOR. DIPP-NH2 is structurally similar to the natural endomorphins, so it can bind DOR through similar mechanisms. The DIPP-NH2 interacts with the Met132, Tyr129, Val217, Ile277, and Trp284 on the DOR. Moreover, one of the two methyl groups on DIPP-NH2 engages Val281 and Ile277. Finally, a salt bridge forms between the DIPP-NH2 N-terminus and Asp128, and this salt bridge is crucial for opioid receptor ligand recognition. The Whitefish Bay High School SMART team (Students Modeling a Research Topic) is modeling DOR using 3D printing technology. DIPP-NH2 may be the basis of a non-addictive painkiller, which would be a significant advancement toward alleviating the major societal and financial problem of opioid addiction.
Fertilizer is an essential component of agriculture globally that is artificially produced through the Haber-Bosch process. This process requires energy to generate temperatures of 400-500 °C and pressures of 15-25 MPa to reduce N2 to NH3. The greenhouse gas CO2 is produced as waste in this reaction. In nature, bacteria in plant root nodules reduce N2 into NH3 catalyzed by nitrogenase. Nitrogenase is a complex comprised of two proteins: a heterotetrameric MoFe protein, and two heterodimeric Fe proteins bound on each end. The MoFe proteins consists of two 491 residue α-subunits and two 522 residue β-subunits. The Fe proteins are bound to the exterior of the MoFe protein creating two mirrored functional halves. In an ATP facilitated process, the Fe protein captures an electron using an iron metallocluster, then donates an electron to the molybdenum/iron metallocluster in the MoFe protein. Electrons are moved within the MoFe protein to the active site. The two halves of the protein alternate in a coordinated manner, transferring one electron at a time until eight electrons are transferred. The electrons then reduce the N2 substrate into 2(NH3)+ H2. The Westosha Central SMART (Students Modeling a Research Topic) Team has created a 3D model of nitrogenase highlighting the metalloclusters and how the complex assembles/disassembles. Understanding how this protein functions may allow mass production of ammonia through a biological process reducing the dependency on the Haber-Bosch process therefore reducing CO2 emissions.
Hemoglobin is an essential protein in red blood cells that carries oxygen from the lungs to cells. Our model tells the story of how a single point mutation affects the ability of hemoglobin to bind oxygen by altering its physical structure. This substitution-type mutation causes the amino acid at position 6 in the beta-chain to change from a negatively charged amino acid to a hydrophobic amino acid. The hydrophobic amino acid causes hemoglobin to take on a sickle shape and reduces its affinity to bind oxygen. Doctors and scientists are developing new cures for this disease using gene editing technology. Our story and model explore the relationship between the structure and function of hemoglobin in the context of sickle cell disease.

Zika virus, or ZIKV, a mosquito-borne pathogen, is a current public health concern due to its link to microcephaly and Guillain-Barré syndrome. A flavivirus, ZIKV contains an RNA genome translated using the host cell's protein synthesis machinery. The 5' end of the viral RNA possesses a "cap" of methylated bases that protect it from being destroyed by the host's immune system. This cap is produced by a virally-encoded methyltransferase enzyme, the NS5 methyltransferase (MTase). Since the 5' RNA cap is required for viral reproduction, inactivating the NS5 MTase with a small molecule inhibitor should be a viable treatment for ZIKV infections. The NS5 MTase transfers CH3 groups from the ubiquitous methyl donor molecule S-adenosylmethionine (SAM) to specific positions on bases at the 5' end of the viral RNA. Based on the binding mode of SAM observed in a crystal structure (5KQR), an analog of SAM was developed that could inhibit the enzymatic activity of the MTase. SAM binds in a pocket composed of Ser56, Arg84, Trp87, Thr104, Lys110, His111, Glu111, Asp131, Val132, Phe133, Asp146, and Ile147. The Grafton SMART (Students Modeling A Research Topic) Team has modeled the NS5 MTase with either SAM or the hypothetical inhibitor MO2 bound using 3D printing technology. Models with such compounds bound to the enzyme provide information that might help increase the potency of potential inhibitors and improve their selectivity for the ZIKV MTase.
Neuroglobin’s Protective Role in Ischemic Stroke
Greenfield High School
Poster #9

Authors: Jorge Andrade, Deven Jakubowski, Joanie Kierzek, Cora Libecki, Jade Lunar, Melody Ly, Gabby Rakestraw, Alexis Tessmer, Keely Veihmeyer
Teacher: Julie Fangmann

Stroke is the second most common cause of death, with cerebral ischemia causing 85% of strokes. Cerebral ischemia is a condition where the brain has inadequate blood supply. Less than five minutes of oxygen deprivation leads to neuronal cell death, harming brain structure and function. Neuronal hypoxia increases expression of a globin protein, neuroglobin (Ngb), near the hypoxic area. Ngb is a neuroprotective monomer made of 151 amino acids forming a typical globin fold with eight alpha helices. The Greenfield High School MSOE Center for BioMolecular Modeling MAPS Team used 3-D modeling and printing technology to examine the structure-function relationship of Ngb. Ngb has a heme group consisting of a porphyrin ring and an iron atom. The iron is hexacoordinated with the heme at four locations, with Ngb’s distal residue His64, and with Ngb’s proximal residue His96. The heme sits in a hydrophobic pocket formed by distal residues (His64, Phe28, Phe42, Tyr44, Lys67, and Val68) and proximal residues (His96, Leu92, Val99, Val101, and Phe106). Under normal conditions, oxygen binds to Ngb’s iron atom, keeping the brain oxygenated. Cerebral hypoxia, as occurs in ischemic stroke, causes neurons to die and release oxygen, reactive oxygen species (ROS), and reactive nitrogen species (RNS). RNS and ROS are toxic byproducts of nitrogen and oxygen metabolism, respectively. Accumulation of RNS and ROS can damage DNA, RNA, and proteins and lead to cell death. Ngb protects surviving neurons by gathering RNS and ROS, allowing these byproducts to be converted into usable materials. Neuroglobin has a large cavity near its heme, formed by interactions between Val71 and Ala74, Leu85 and Tyr88, and Leu136 and Tyr137. This cavity allows ligands to access the iron for binding, either storing it for use later (oxygen) or removing it to be converted to prevent damage (RNS and ROS). The further study of neuroglobin and its protective nature could lead to the development of treatments for ischemic stroke.

Modeling methemoglobinemia and the molecular mechanism of nitrate poisoning (from contaminated well water)
Valders High School
Poster #18

Authors: Lauren Erdman, Ireland Fenlon, Heather Hickmann, Maddie Kinscher, Jacob Krim, Jesse Linsmeier, Jacob Pattee, Madison Storm, Evelyn Tapia-Campuzano, Danielle Visser, Trevor Wenzel, Maddie Zutz
Teacher: Joseph Kinscher
Mentors: Dr. Rebecca Abler & Dr. Richard Hein
University of Wisconsin-Manitowoc

NADH-cytochrome b5 Reductase (CytB5R), an enzymatic protein found in mammalian erythrocytes, catalyzes the reduction of ferric (Fe+3) methemoglobin to ferrous (Fe+2) hemoglobin. High levels of methemoglobin in infants, caused by nitrate poisoning and naturally low levels of erythrocyte CytB5R, can result in methemoglobinemia or blue baby syndrome. Methemoglobinemia is caused by the inability of Fe+3 methemoglobin to carry oxygen throughout the bloodstream. Three domains of CytB5R make possible the transfer of two electrons from NADH to FAD resulting in fully reduced FADH-. FADH- then transfers electrons to one-electron acceptors such as Fe+3 methemoglobin resulting in Fe+2 hemoglobin. Ngb protects surviving neurons by gathering RNS and ROS, allowing these byproducts to be converted into usable materials. Neuroglobin has a large cavity near its heme, formed by interactions between Val71 and Ala74, Leu85 and Tyr88, and Leu136 and Tyr137. This cavity allows ligands to access the iron for binding, either storing it for use later (oxygen) or removing it to be converted to prevent damage (RNS and ROS). The further study of neuroglobin and its protective nature could lead to the development of treatments for ischemic stroke.
Fuel Alternatives: The use of E. coli NADPH-dependent aldehyde reductase YqhD in a cellulosic process to generate butanol

The Independent School
Poster #17

Authors: Chase Bowman, Dylan Vance, Julia Fetters, Kennedy DeVore, Malar Muthukumar, Maria Chen, Reid McConnaughey
Teacher: Lin Andrews
Mentor: Katie Mitchell-Koch, PhD
Wichita State University, Department of Chemistry

The overall relevance of the E. Coli enzyme YqhD aldehyde reductase is its effect on the production of butanol, a type of biofuel. Butanol can be used in higher percentages in fuel blends than ethanol. Butanol derived from biomass offers an attractive alternative to ethanol, which require extra cultivation of land and is derived from food sources. Butanol, however, uses waste products. Yeast can be used to produce the fuel. In making butanol from hexoses (6-carbon sugars derived from biomass), two carbons are lost, making the formation of butanol less atom-efficient than other biofuels. The Independent School MSOE Center for BioMolecular Modeling SMART Team used 3-D modeling and printing technology to examine the structure of Escherichia coli NADPH-dependent aldehyde reductase YqhD. Three critical parts of the protein are the cofactor binding cleft, the substrate access channel, and zinc ions. The cofactor binding cleft holds NADPH in position, the substrate access channel funnels substrate to the active site, and the zinc ions interact in the active site with the substrate. Interactions between these three particular parts of the YqhD protein lend to the final steps of the creation of butanol.

The Role of MeCP2 Mutations in a Reg-Rett-Able Syndrome

Hartford Union High School
Poster #10

Teacher: M Arnholt
Mentor: G Makky, PhD
Marquette University

Rett Syndrome affects about one in every 10,000 to 15,000 births. It is a genetic neurodevelopmental disorder that mainly occurs in females. Affected males die in infancy because the syndrome exhibits an X-linked dominant pattern of inheritance. Rett Syndrome is caused by mutations in the X-linked Methyl CpG binding protein 2 (MeCP2) coding gene. MeCP2 is necessary for epigenetic regulation of gene expression. This protein represses transcription by acting as a molecular bridge between methylated DNA and a complex of co-repressor proteins including histone deacetylases and Sin3A. Mutations of MeCP2 cause overexpression of several genes during brain development. MeCP2 is a 52-kDa protein with two functional domains: the transcriptional repressor domain (TRD) and the methyl-CpG binding domain (MBD). Within the MBD, mutations of Arg106, Arg133, Phe155, and Thr158 result in a decreased binding affinity of MeCP2 to methylated DNA: 2-fold for mutated Thr158 and 100-fold for the remaining mutated amino acids. The MBD has three beta sheets with Thr158 located on the c-terminal end. Here, hydrophilic residues interact specifically with the methylated DNA. The Hartford Union High School SMART (Students Modeling A Research Topic) Team designed a model of MeCP2 using 3D printing technology to represent the MBD-methylated DNA complex. The model highlights the amino acids involved in the interaction between MeCP2 and methylated DNA. Modeling the structure of MeCP2 allows for a more detailed understanding of the interaction between MeCP2 and DNA. This information will be crucial for designing treatments or interventions to improve the quality of life for Rett syndrome patients.
Leptin and PACAP: Possible Co-op?
Kettle Moraine High School
Poster #11

Authors: Mahi Gokuli, Ethan Helfenstein, Kathryn Hallada, Kelsi Morris, Liam Mulcahy, Autumn Saunders, Divyank Sharma, Aaron Smet, Justin Smet
Teacher: Melissa Kirby
Mentor: SuJeean Choi, PhD
Marquette University

More than one-third of American adults are obese, and obesity-related conditions including diabetes, hypertension, and stroke are among the leading causes of preventable deaths. Leptin is a hypophagic hormone secreted by fat cells, thought to regulate satiety. The Ile14 residue in leptin is crucial for the interaction between leptin and its receptor. Leptin helices A and C interact with the CRH2 domain of the leptin receptor. Mutations to Ile14 disrupt the docking conformation in a manner that prevents helices A and C on leptin to position parallel with CRH2 thereby, affecting the binding efficiency. Mutation to the Ile14 residue results in excessive feeding and weight gain. The neuropeptide pituitary adenylate cyclase activating polypeptide (PACAP) produces identical hypophagia via the hypothalamic ventromedial nuclei (VMN) to that of leptin. The proximity of leptin and PACAP receptors combined with their functional similarity suggest they could collaborate to induce hypophagia through a shared intracellular signaling cascade. By identifying critical molecular sites necessary for leptin action, we may better understand how PACAP and leptin receptor signaling are linked, whether changes to the residue also alters PACAP signaling and the degree to which it contributes to obesity or eating disorders. The Kettle Moraine High School SMART (Students Modeling a Research Topic) Team has modeled leptin using 3D printing technology to investigate structure function relationships. Inquiry into leptin and PACAP interactions may reveal the nature of interdependency between neural and peripheral energy-regulating systems in the VMN, new applications of hypophagic drugs, and the biological cause of obesity.

Mitochondrial Fis1’s N-Terminal “Arm” Orientations
St. Joan Antida High School
Poster #16

Authors: J. Allen, S. Kopacz, S. Mitchell
Teachers: K. DiFonzo, C. McLinn, A. Montgomery
Mentors: J. Egner, BA and A. Bakkum, BA
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Mitochondria provide over 90% of the energy needed to maintain healthy cell function. Mitochondrial fission is essential to mitochondrial health. Mutations in mitochondrial proteins are implicated in diseases such as heart disease and diabetes. Current research is exploring the role of Mitochondrial fission protein 1 (Fis1) and key interactions with Dynamin related protein 1 (Drp1), and Mitochondrial dynamics protein of 51 kDa (MiD51). Preliminary data suggests that Fis1 competitively binds MiD51, relieving MiD51 inhibition and indirectly stimulating Drp1 activity to activate mitochondrial fission. These processes assist in removal of damaged mitochondria and support apoptosis during high cellular stress levels. Potential ligands that interact with Fis1 have been found to be MiD51 and Drp1, which may be regulated by Fis1’s intramolecular interactions. Using 3D printing technology, the St. Joan Antida SMART (Students Modeling a Research Topic) Team modeled cytosolic domain of Fis1 and the twice-repeated tetratricopeptide (TPR) repeat motif which is the predicted binding interface for Fis1-MiD51. TPR1 contains helices 2 & 3 and TPR2 contains helices 4 & 5. Residues 1-8 of the N-terminal arm are modelled in two orientations – “arm open” and “arm closed” – representing potential blocking of the active site within the concave pocket formed by TPR1&2 of Fis1. Current research hypothesizes sidechains of Asn6 and Arg83 to be responsible for “arm” orientation blocking the active site. Elucidating the role of Fis1-MiD51 axis in mitochondrial fission in the context of healthy and diseased models can lead to developing better therapeutics and treatments for heart disease and diabetes.
CHIP is a Neuroprotective Ubiquitin Ligase
St. Dominic Middle School
Poster #15

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CHIP (C-terminus of HSC interacting protein) is a neuroprotective ubiquitin ligase highly expressed in the brain. CHIP plays a crucial role in the ubiquitin proteasome system (UPS), a process that tags proteins with polyubiquitin chains targeting them for degradation. CHIP helps regulate protein quality control through its E3 ligase activity. As an E3 ligase, CHIP acts as a scaffold binding the E2 (ubiquitin conjugating enzyme) and the molecular chaperone Hsp90. CHIP aids the transfer of ubiquitins from E2 to a target protein bound to its chaperone, Hsp90. The polyubiquitin chain tags proteins for proteasomal degradation. The St. Dominic SMART Team (Students Modeling A Research Topic) modeled the homodimer CHIP using 3D-printing technology. Each monomer contains a tetratricopeptide repeat (TPR), helical hairpin (HH), and a U-Box domain. The N-terminal TPR domain binds the molecular chaperone Hsp90 using the sidechains Phe38, Lys73, Asn66, Leu69, Phe100, Lys96, Phe99, Phe132, and Asp135. The C-terminal U-Box binds E2 ubiquitin conjugates using Asp230, Phe238, Ile236, Val271, and Arg273. The HH domain is a long straight helix in one monomer but bends at a 90° angle in the other. Autosomal recessive mutations in the TPR, HH, and U-Box domains cause neurodegeneration in multiple areas of the brain leading to various combinations of symptoms such as ataxia, dementia, hypogonadism, seizures, and loss of language. Further research of CHIP’s structure and function could also lead to new understanding more common neurodegenerative diseases such as Alzheimer's and Parkinson's.

Fix the Wrecks, RecA
Madison West High School
Poster #12

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Accurate and complete DNA replication is essential to all life. However, collisions and obstacles that lead to DNA breaks are common. There are many proteins that have the essential job of correcting these mistakes. Some do this by trimming the broken ends of the strands and reconnecting them. RecA instead assists a more accurate method of repair called homologous replication. In this process, RecA binds to the broken strand of DNA and locates the same sequence on an intact duplicate strand. The ssDNA bound RecA then catalyzes a synopsis reaction between the filament and homologous double stranded DNA (dsDNA). Other proteins add complementary bases to synthesize a second copy of the missing section of the original single stranded DNA (ssDNA). Finally, the strands are separated to form a complete DNA and restore the missing information (Cox, MM. (2007)).

Homologs of RecA are found in almost all organisms and are a critical part of genome maintenance and DNA repair. It is crucial for accurate homologous recombination which, when done incorrectly can lead to cancer and genome instability (Chen, Z., et al (2008)). When Rad51, the human homolog of RecA is dysregulated, it increases chances of cancer. Specifically, Rad51 is underexpressed in 100% of renal cell carcinomas (Liu, S., et al (2016)). Understanding the implications of cell repair regulation may allow for future cancer treatments.

The Madison West High School SMART (Students Modeling A Research Topic) Team is Modeling RecA bound to DNA to learn more about the process of homologous recombination. Specifically, how the RecA filament interacts with DNA. Current science dictates that three RecA molecules interact with each nucleotide triplet in a DNA strand (Chen, Z., et al (2008); PDB: 3CMX), which we will be investigating in more detail. DNA replication is necessary for life, and when breaks occur in the DNA, it needs to be repaired. RecA recognizes the DNA damage, and performs homologous recombination. Understanding this process may aid in the development of novel cancer therapies, allowing for more cost-effective treatments.
More than 1.2 million people in the United States are living with the HIV virus, with about 50,000 new cases each year. All viruses, including HIV, need the viral protein Integrase, which integrates the viral genome into the host genome for replication. The integrated DNA is then accessible to make more viruses or is able to stay dormant until the best opportunity to activate, generating viruses. Currently, the reaction mechanism of HIV DNA insertion into host DNA is poorly understood, and exactly how this works is key to understanding how the whole of a virus, like HIV, functions. The Monona Grove High School SMART (Students Modeling a Research Topic) Team is modeling Integrase found in a prototype foamy virus to better understand how the mechanisms of strand transfer are carried out and how this could relate to the HIV virus found in humans. By studying the post-catalytic strand transfer structure of Integrase1, PDB 3OS0, we will be able to better understand reaction intermediates and host DNA sequence preference of the HIV DNA integration process. It is important to study viral DNA integration because it will aid in understanding HIV, as well as other viruses, and potentially help design more, novel drugs that block this integration and even cure retroviral infections like HIV. This infection is a global problem from a virus that is constantly evolving, and studying integrase is just one step to further solving this epidemic.