Fantastic Molecules and Where to Find Them:
The Search for New Drugs to Treat Type II Diabetes

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This curriculum unit is recommended for:
All levels of Project Lead the Way: Principles of Biomedical Science

Keywords: Science, Biology, Biomedical PLTW, Scientific thinking, Drugs, Drug therapy, Research, Development, Diabetes

Teaching Standards: See Appendix 1 for teaching standards addressed in this unit.

Synopsis: Diabetes is one of the greatest health concerns in the United States. This disease robs people of their vision, healthy organ function, emotional health, and overall quality of life. Although there are lifestyle modifications that can alleviate or reverse type 2 diabetes, there are some patients that are unresponsive to traditional treatments. The purpose of this curriculum unit is to teach students how type 2 diabetes is clinically diagnosed, what is occurring at the cellular level, and how novel medications can be investigated. Students will learn about the phases of a clinical trial by reading about current pharmaceutical research, and model a clinical trial with a fictional drug. Students will be presented with fictional patients, and investigate the root causes of the signs and symptoms of diabetes. They model glucose tolerance testing and blood-insulin level testing to diagnose these patients, track the lifestyles of these individuals to determine environmental impact, and investigate types of treatment.

I plan to teach this unit during the coming year to 60 students in Project Lead the Way: Principles of Biomedical Science in grades 9-12.

Introduction

> *"How would you like to live in Looking-glass House, Kitty? I wonder if they'd give you milk in there? Perhaps Looking-glass milk isn't good to drink—"*
>
> Alice in *Through the Looking Glass*[1]

In Lewis Carroll's story, Alice looks into the mirror hanging over the hearth in her home's parlor, and concocts a universe for the house inside the mirror. Alice begins by offering an enticement to her cat to "pretend" with her, but amends her offer with reservations about the healthfulness and/or taste of Looking-glass milk…and those reservations may have great merit. On the molecular level the stereoisomers of a lot of the components of milk, such as lactose and casein, could have differing physical and chemical properties significant enough to not only make Looking-glass milk taste very different from that of our world, but possibly render it toxic. [2] Alice starts her adventure shortly after making this speculation, and was too busy to carry out any experimentation once she went through the looking glass. In the real world, strange new substances are possible cures for diseases, and drug researchers are very concerned with knowing if "the milk isn't good to drink". Novel molecules might affect cell processes in the treatment of diseases and disorders, and must researchers must conduct thorough testing to demonstrate the effectiveness and safety of a proposed drug before it can be released for availability to the public.

Drug companies want to target the largest possible population of consumers to justify the investment made in lengthy, and often fruitless, research studies into molecules that they consider potentially useful. Enter Type II Diabetes. According to the Centers for Disease Control, 23.1 million Americans had diagnosed diabetes in 2015. (National Diabetes Statistics Report, 2017, 2017) Diabetes is epidemic in the United States, and takes a toll on the individual patient physically and emotionally. As a country, it has a significant economic impact. Costs associated with diabetes, including direct medical costs and loss of productivity, totaled $245 million in the U.S. in 2012. Effective, novel treatments for diabetes have the potential to yield great profit for the pharmaceutical industry. The process that takes a new drug from the lab bench to the pharmacy counter takes years, and is designed to protect the public.

Rationale

Project Lead the Way (PLTW) is a national STEM program with arms in engineering, computer sciences, and biomedical science.[3] I teach two of the biomedical courses. Goals of PLTW include exposing students to using laboratory tools and equipment, training students to think as researchers, and developing problem-solving skills, critical thinking, and communication of science. PLTW provides a set of objectives and lesson plans that are interpreted and altered by the instructor, then presented to students. The problem is, PLTW is a national program, and unfortunately a lot of the material has been posted online, allowing students to access completed projects and practice work without having to put in their own effort. In other words: they cheat. One of my goals is to present students with unique lessons that meet the objectives set by PLTW. One of the glaring omissions in the PLTW curriculum is a purposeful study of drugs and how they are developed. These students want to be medical professionals, and they need to have an understanding of the purpose of pharmaceuticals, what they actually are, and how they are

developed and regulated. One of the units in the PLTW: Principles of Biomedical Sciences is titled “Diabetes”. This curriculum unit is an effort to provide a more in-depth look at drug research by tying it to the required objectives for diabetes.

School/Student Demographics

I teach at large urban public high school that serves students in grades 9-12, with approximately 2500 students attending. Our school is often described as “diverse and high achieving, reflected by our demographics: 63% African American, 18% Caucasian, 9% Hispanic and 6% Asian. 45% are classified as economically disadvantaged. Our graduation rate consistently hovers around 95%. Each subject area in the school has a general department which is divided up by grade level or specific course within that subject area. The classes I teach are mixed grades in the Biomedical Academy within the Career and Technical Education department of my high school.

This course is classified as an “honors” class. Most of the students I teach are above average academically, and a majority have chosen to take the class because they are interested in careers in medicine. There are some lower achieving students that choose to take the class.

Short term, my goals are to prepare these students to take the PLTW Principles of Biomedical Science end of course exam, which is prepared and securely administered through PLTW. Students are eligible for credit through University of Iowa and other colleges and universities based on their EOC scores. Long term, I want them to be able to move through the rest of the four year PLTW program successfully and accumulate college credits so that they can be well armed for the college application process and be accepted into the programs of their choice. Since most of these students elected to take this course specifically because they want a medical career, the work they do in this course can be invaluable!

Unit Goals

Students will develop an understanding of ligands and target proteins on the surfaces of cells by doing an in-depth study of the insulin-glucose connection. Students will draw conclusions about the connections between the problems at the cellular level in diabetes and the gross signs and symptoms seen at patient presentation. This will satisfy the National Science Education Standards Standard C: Life Science and National Health Care Cluster Foundation Standards Accountability Criteria 1.2: Diseases and Disorders, and Next Generation Science Standard HS.LS1.2 - From Molecules to Organisms: Structures and Processes.

Students will be presented with fictional patients, and investigate the root causes of the signs and symptoms of diabetes. They model glucose tolerance testing and blood-insulin level testing to diagnose these patients, track the lifestyles of these individuals to determine environmental impact, and investigate types of treatment. This will satisfy the National Science Education Standards Standard F: Science in Personal and Social Perspectives and Accountability Criteria 1.3: Medical Mathematics.

Students will model the development and testing of novel molecules for treatment of type 2 diabetes by staging the different phases of a drug trial for a fictional drug. This will address Next Generation Standard HS.PS2.6 - Motion and Stability: Forces and Interactions.

Background Information

Diabetes

The energy coin of human cells is adenosine triphosphate (ATP). ATP is produced by multiple pathways within cells, but the easiest pathway is aerobic respiration of glucose. Aerobic respiration occurs in the mitochondria of cells, and requires glucose and oxygen. Oxygen is obtained when it enters the blood from the lungs and is carried to all the tissues of the body. It enters individual cells via simple diffusion, and is directed toward the mitochondria in the cytoplasm from there. The logistics of glucose transport are a bit more complicated. First, food products containing glucose must be digested, and the glucose is absorbed into the blood stream via the lining of the small intestine. The blood transports the glucose to individual cells, but those cells must express GLUT4 receptors in their cell membranes order to take in the glucose. (Huang, 2007) Until needed, GLUT4 is stored in vesicles in the cytoplasm of cells (Figure 1)[4]. Expression of GLUT4 does not occur unless triggered by a signal transduction cascade (STC) is induced within the cell by interaction of insulin with an insulin receptor on the surface of the cell (Figure 2).

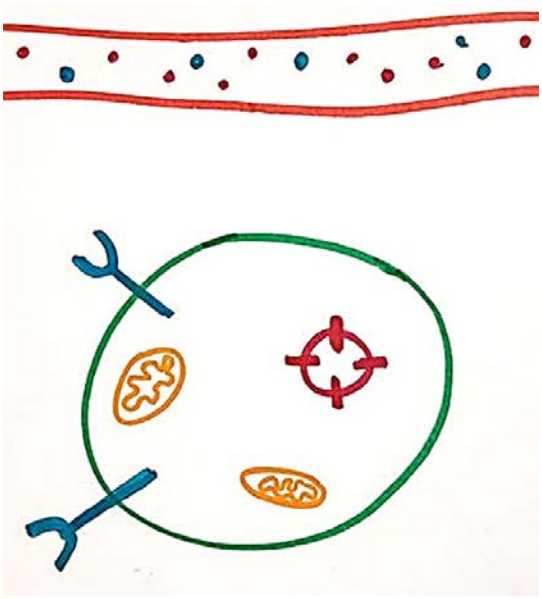

Figure 1: Cell and blood vessel. Prior to the signal transduction cascade, GLUT4 is stored in a vesicle (magenta) in the cytoplasm.

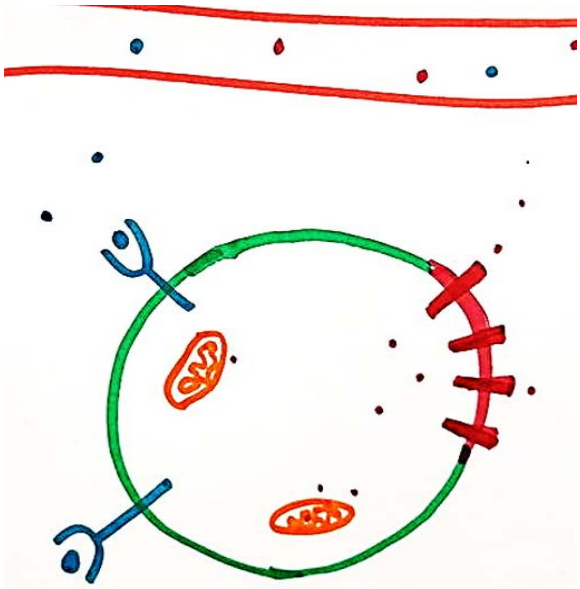

Figure 2: Cell and blood vessel. Once insulin binds to insulin receptors (blue) in the cell membrane (green), the STC prompts the GLUT4 vesicle to merge with the cell membrane, allowing glucose to enter the cell.

So, how do we get insulin involved? In response to rising glucose levels in the blood, beta cells in the pancreas produce and secrete insulin. It enters the blood stream almost simultaneously with glucose from the intestine, and travels to individual cells. It binds to insulin

receptors (IR) on the surface of the cell to induce the STC. Once GLUT4 is integrated into the cell membrane, glucose can enter the cell and be directed to the mitochondria, where it is oxidized to produce ATP molecules. (Huang, 2007)

Diabetes mellitus occurs as a result of glucose being unable to leave the blood stream and enter cells of the body. There are several types of diabetes. Type I diabetes is sometimes called "Juvenile Diabetes", because its onset frequently occurs in childhood. Type I diabetes is an autoimmune disorder in which the body's own white blood cells mistakenly attack and destroy beta cells, where insulin is produced. It takes several years for the disease to fully manifest, but eventually the beta cells are completely destroyed, and the patient can no longer produce insulin. Lack of insulin means that glucose cannot enter cells, and sufficient ATP cannot be made to keep up with the cell's energy expenditure. This is responsible for the high glucose levels in blood, which leads to increased osmotic pressure on cells, causing thirst and frequent urination. (Type I Diabetes, 2017) Since glucose is not being taken in, it is extracted from the blood by the kidneys. The glucose can be detected in the urine clinically (or by the very, very outdated "taste test")[5]. The high osmotic pressure due to all this extra glucose is hard on the kidneys, and can lead to kidney damage and failure. Cells have to depend on alternate pathways to make ATP, such as lipid and protein metabolism. This leads to weight loss, and complications such as ketoacidosis. (Type I Diabetes, 2017)

Type II diabetes has historically been considered "adult onset", but in the last two decades has become alarmingly common amongst children. Type II diabetes has a different course of expression. At first, the cells of the body become resistant to insulin. The reasons for this are poorly understood. Research is focused on possible interruptions to the signal transduction cascade, or possible changes in shape to insulin receptors (Kolterman, 1981). Less glucose is able to enter cells and remains in the blood. The pancreas tries to force the issue by making more and more insulin. A typical GTT/insulin panel for a type II diabetic at this stage reveals elevated levels of both glucose and insulin for extended periods of time after glucose consumption. Over time, the pancreas "gives up", and insulin levels do not rise significantly after glucose consumption, giving the patient a panel that looks similar to that of a type I diabetic. Whereas type I diabetes is an autoimmune disorder, the onset of type II diabetes is quite often a result of lifestyle choices.

Diabetes, as with any disease, has identifiable risk factors. There are some risk factors that are part of individual control and are modifiable, such as poor diet, and there are risk factors that cannot be modified, such as genetics. Risk factors for Type 2 diabetes include impaired glucose tolerance, age over 45, family history of diabetes, sedentary lifestyle, obesity, low HDL cholesterol, high triglycerides or blood pressure, having gestational diabetes (or a baby over 9 pounds), and certain ethnicities (African, Latino, Asian and Native American ancestry). (Prediabetes and Insulin Resistance, 2009) Risk factors for Type 1 diabetes are a bit sketchier. There are some genetic markers for the disease, and it seems to have a familial component. Reported incidence of type I diabetes tends to increase geographically as you travel further from the equator.

Type I diabetes treatment requires replacement insulin, and seeks to limit the impact of the disease on tissue and organs. To this end, patients keep careful food diaries and work to keep

rested and well hydrated. Type II Diabetes treatment focuses largely on modifying lifestyle as well as insulin replacement (as needed). These modifications can lead to reversal of the disease. However, patient compliance with dietary planning and exercise routines can be difficult to establish.

Developing a Drug Therapy

The students will investigate how a new drug for the treatment of type 2 diabetes could be developed for the market. Given the number of people in the U.S. who are diagnosed with type 2 diabetes, and the impact it has on a family's finances and a patient's long term health and quality of life, a "quick fix" in the form of a drug to allow normal glucose transport in these patients would be of great benefit.

Drugs are substances that alter cell function and are formally defined as substances intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease". (Drug Approvals and Databases - Drugs@FDA Glossary of Terms, 2017) A substance can be designated a drug when it has been formally recognized in a professional publication or formulary. Insulin itself is a drug when administered to insulin-dependent diabetics. In the case of type 2 diabetes, the interruption of the signal transduction cascade seems to cause the failure of GLUT4 translocation and glucose uptake. There are multiple proteins at work in the STC, and some of them, such as Akt[6] have been shown in mouse models to be of particular interest in the type 2 diabetic. Finding molecules that can enhance or correct the work of these proteins is a good starting place for drug research.

Preclinical Phase

The road to an interesting molecule becoming a drug starts at the lab bench. The "Preclinical" phase involves identification of the molecule of interest, preparation of the molecule, and testing on *in vitro*, *in vivo*, and animal models. The purpose of the preclinical phase is to verify that the molecule will not be toxic to humans, and to determine an appropriate dosage that can be used in the human trials. Practical matters, like the preparation protocol of the molecule and its method of delivery, are determined. Testing for toxicity will require building a profile of the drug's pharmacokinetics (what the body does with the drug). This profile will include how well the drug is absorbed on delivery, its bioavailability, how it is distributed to body cells, and how it is metabolized and excreted. The pharmacokinetics profile is known by the acronym "ADME". (Doogue, 2013)

A is for absorption. Testing will indicate how well the drug enters the bloodstream. This is described as the drug's *bioavailability*, and is measured as a percentage of the drug that actually reaches the bloodstream. Absorption depends to a great extent on how the drug is administered. Drugs that are injected directly into the blood have 100% absorption. However, injection is inconvenient, and may lead to a decrease in compliance on the part of the patient (who likes getting a shot?). Oral administration is considered the preferred route of administration, but the drug has to be able to survive exposure to digestive juices of the alimentary canal, and have the correct chemical properties to pass through the wall of the gut into the bloodstream. This decreases the bioavailability of the drug. Oral drugs often have

bioavailabilities below fifty percent. (Stevens, Meeting #8: Absorption and Bioavailability, 2017)

D is for distribution. Distribution is the transfer of the drug from the blood to the tissues in order to reach individual cells in the tissues. The drug has to be able to move across capillary walls and into the interstitial fluids, and then across the cell membrane into the cytoplasm of the cell. This will depend on the molecular weight of the drug (how big the molecule is), and the lipid solubility of the substance. Molecules that are too large may be trapped in the blood because they cannot get across the capillary wall, and will be cleared out of the body by the kidneys before they have any chance of performing their intended action on the cells. If the molecule is too polar, it won't be able to penetrate the phospholipid bilayers that make up the cell membranes. On the other hand, if it isn't polar enough, it won't be water soluble….and water makes up the majority of the interstitial fluid and cytoplasm! (Amanda, 2011)

M is for metabolism. This is the breakdown of the drug, primarily by the liver. Once the drug enters the circulatory system, it is going to pass through the liver. The liver's job is to look at molecules in the blood, and figure out how to alter them. This involves enzymatic reactions that break pieces off of a molecule, and then attach new groups. These actions make the molecules smaller, and increase their solubility in water for clearance by the kidneys. From the researcher's point of view, these metabolites need to have the intended effect on the tissues. A drug that is shown to be effective *in vitro* may not do well at all in animal trials because it loses important components when it passes through the liver. (Stevens E. , 2017)

E is for excretion. The kidneys are the primary organs of excretion. Blood wastes are extracted in the nephrons, water is added, and the waste passes out of the body in the form of urine. Some drugs can be found in urine in their original form or as metabolites after they are acted on by the liver. Drugs and their metabolites may also show up in tears, sweat and saliva. (Amanda, 2011) The drug of interest needs to be able to stay in the body long enough to be moved into the tissues so it can have its intended action. Excretion and metabolism together are known as the *clearance* of the drug, and are the main consideration in determining the dosage of the drug that will be needed to maintain an effective concentration in the bloodstream.

Clinical Trials

Drug companies sink huge amounts of money into preclinical trials, and the results can be discouraging. "On average, only one in every 5,000 compounds that drug companies discover and put through preclinical testing becomes an approved drug. Of the drugs started in clinical trials on humans, only 10 percent secure F.D.A. approval". (Emanuel, 2015) In clinical trials, the novel drug is tested for the first time in humans. At this point, a great deal of money has already been invested by the backers of the research, and the drug must make it through even more expensive clinical trials before it can be approved by the appropriate governing body. Each phase weeds out inappropriate molecules before they can move on to the next phase.

Phase 1 trials are carried out on a small sample population (20-100 participants) over the course of several months. The initial phase is to study the safety of the drug, look at dosage and

delivery, and look for side effects. About 70% of tested molecules move through phase I. (Clinical Trial Phases, n.d.)

Phase II trials involve 100-300 participants and can last up to two years. The goals of the phase 1 trial are retained, so that more subtle, long term effects have time to emerge. In addition, the effectiveness of the drug on the target of interest is evaluated. This usually involves a study comparing the drug's effectiveness against that of a placebo. About 33% of molecules move forward from this phase.

Phase III trials last 1-4 years, and the dosing, efficacy, and safety are further studied. 1,000-3,000 participants will be recruited, with specific requirements that may include age, types of prior treatment, and other qualifiers used in participant selection. About 25% of drugs will move forward to phase IV. At this point, the drug is submitted for approval by the Food and Drug Administration's CDER – the Center for Drug Evaluation and Research. CDER evaluates new drugs before sale. CDER takes the data collected by the research institution and reviews it, determining whether the benefits offered by the new treatment outweigh the risks that may be posed by the drug. (How Drugs are Developed and Approved, 2015) CDER checks that the drug does what it is touted to do, and compares the proposed treatment to currently available therapies. CDER recommends FDA approval if it determines that the benefits of the therapy outweigh potential risks for the target population.

Phase IV trials are ongoing, and will be carried out as long as the drug is on the market. The drug can be pulled from the market if it is determined to have detrimental effects not observed in the first three phases, or side effects that are unacceptably magnified over time.

Instructional Implementation

Lesson 1: Diagnosing Diabetes

Essential vocabulary: Type I diabetes, type 2 diabetes, glucose, insulin, blood, glucose tolerance test, pancreas

Essential Questions:

1. What is diabetes? List 5 symptoms.
2. How is glucose tolerance testing used to diagnose diabetes? Be able to interpret Blood Insulin and Blood Glucose levels graphs for diagnosis.
3. How are Type I and Type II diabetes similar? How are they different?
4. What foods contain glucose?

Materials: buffer solutions, pH test paper, bromothymol blue, well plates, capped plastic test tubes, test tube stands, pipettes, color charts, gloves, goggles, computers with internet access.

Know: Students will be given the patient histories and a list of symptoms for three fictional characters: Marina, Agnes and Barney. They will then be given a selected reading explaining what diabetes is, and how it presents. This will be followed by a class discussion of the patients,

and we will make predictions as to whether or not Marina, Agnes or Barney have diabetes, and if so, what type.

Understand: The teacher will give a brief PowerPoint presentation of the purpose of a glucose tolerance test (GTT), and how the results are interpreted. Essential vocabulary and content will be provided and a question and answer session conducted. Students will carry out a GTT using buffers as substitutes for patient serum samples drawn at 0, 30 minutes, 60 minutes, 90 minutes, and 120 minutes. Students will test the "glucose level" of each sample using pH test strips and record their data in a data table. They will repeat this process with a different set of buffers and bromothymol blue to determine the "insulin level" of each sample.

Do: Students will use their data to make graphs on the "Create-A-Graph"[7] website. See Figure 3 for how the graphs should be set up.

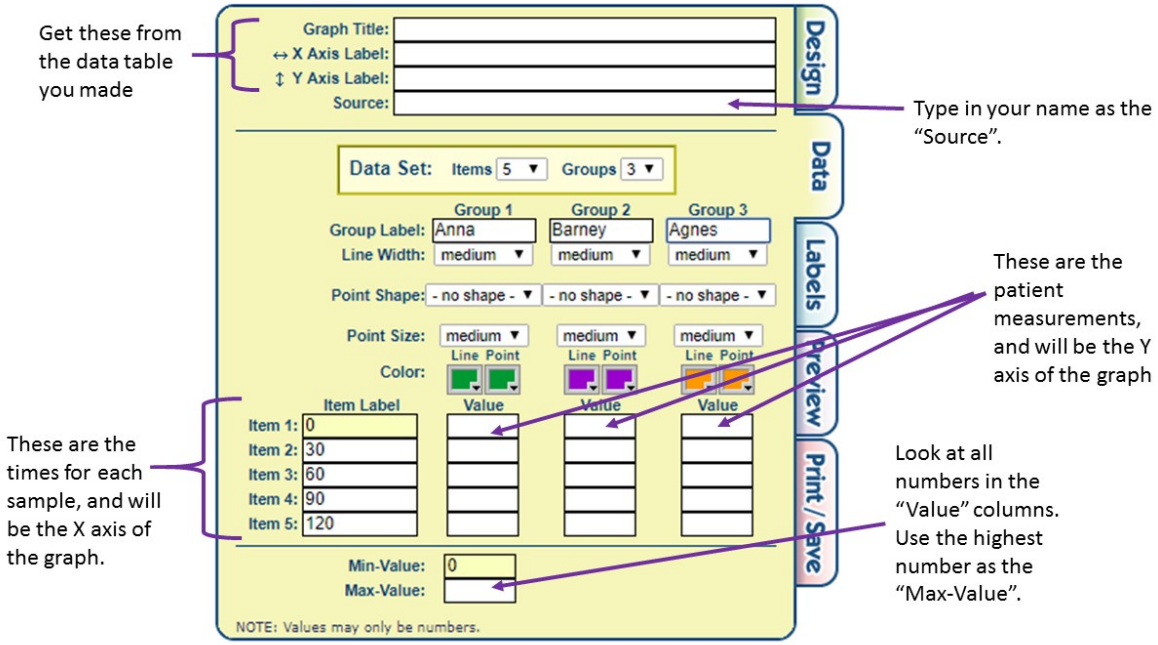

Figure 3: Screen shot from Create-A-Graph illustrating how to set up data from glucose tolerance test and blood insulin test. Labels made by Kari Rhoades.

Assessment: The students will compare the glucose levels of the three patients over time and determine if their predictions made at the beginning of the lesson were correct. They will identify the patients as having normal glucose and insulin activity (Agnes), type 1 diabetes (Marina) or type 2 diabetes (Barney). The students will turn in their graphs with a write up of their assessment of the data for each patient.

Lesson 2: The Physiology of Diabetes

Essential vocabulary: Insulin receptor, GLUT4, vesicle, mitochondria, phospholipid, pancreas, intestinal villi, blood, cell membrane, signal transduction cascade (STC), insulin, glucose, ligand

Materials: Poster or chart paper, markers, pony beads, pipe cleaners, camera, computer with internet access

Essential Questions:

1. Why do your cells need glucose? What do they make from it, and where does this happen?
2. What is the relationship between insulin and glucose?
3. How does insulin assist with the movement of glucose into body cells? Where is insulin made?
4. Explain how disruptions of any part of this pathway could result in diabetes.

Day 1

Know: Students will be given some simple animations to view that describe the roles of insulin and glucose at the cellular level.[8] After class discussion of each of the four videos, students will be given a list of research questions (see below) that they must answer and source. Each student will locate information about how insulin signals a cell to take in glucose from the blood. A minimum of three good sources of information that include diagrams, pictures, and/ or interactive elements that will help them explain the relationship between the two molecules. The students will build a works cited page in APA format. The students will end the period by using the research questions to write out a step-by-step explanation of the events that lead to GLUT4 expression, and how this process becomes dysfunctional in type 1 and type 2 diabetes.

Research questions:

1. What types of food provide glucose?
2. Where is glucose absorbed into the blood stream?
3. Where is insulin produced?
4. What exactly is insulin?
5. What is GLUT4? How is GLUT4 stored inside a cell?
6. What causes vesicles with GLUT4 to rise to the surface of the cell?
7. What happens once GLUT4 is part of the cell membrane?
8. Does insulin ever enter the cell?
9. Why doesn't this process work in Type 1 diabetics?
10. Why doesn't this process work in type 2 diabetics?
11. What is glucagon? What does glucagon do?
12. Where is glucagon made?
13. What triggers the release of glucagon?

Day 2

Understand: Using information gathered to answer the research questions, students will work in pairs to design a poster/model with moveable parts that they can use to explain the process by which insulin interacts with insulin receptors to trigger events that lead to the expression of GLUT4 on the cell membrane. Students will use markers and poster paper or chart paper to draw the static elements, such as blood vessels, organelles, insulin receptors, and the cell membrane. Beads and pipe cleaners will be used to make moveable parts, such as insulin, glucose, and the GLUT4 vesicle. The following elements must be accounted for in the poster/model.

- Glucose transport proteins (GLUT4)
- Cell membrane (phospholipid bilayer)

- Glucose
- Blood (blood vessel)
- Mitochondrion
- Insulin
- Insulin receptors
- Intracellular vesicle

Day 3
Do: Students will take a series of still photos of their posters as they move the different elements to illustrate the process that leads to glucose uptake. Once the pictures are taken, the students will be given the choice of uploading the pictures into PowerPoint and providing text to explain what is happening in each picture, or uploading the pictures into Microsoft MovieMaker and recording verbal narration to explain the process.

Assessment: Students will submit their research, works cited, and research write-ups for teacher evaluation. The PowerPoints and videos will be shown to the class as a whole for peer evaluation. Students will be given rubrics and training in how to use them for the peer evaluations.

Lesson 3: Developing Treatments for Diabetes

Day 1
Essential vocabulary: Preclinical trials, clinical trials, pharmaceuticals

Materials: NY Times article[9], computers with internet access

Essential questions:
1. What drives drug research?
2. What ethical concerns are raised by a drug company's pricing decisions?

Know: Students will participate in a think-pair-share activity.[10] Students will read the NY Times article and be given the prompt "As you read, think about the cost of drug research, and how it is passed on to the consumer".

Understand: Student's will divide up into groups of three or four, and will share one thing they learned from the article with each other. On their papers, they will record each other's responses, and as a group talk about what they think is fair or unfair about how drug prices are determined, and one potential solution. The teacher will circulate and support and encourage student interactions and ideas. After an appropriate amount of time, the teacher will expand the discussion to the whole class, asking for groups to share their thoughts on the ethical issues surrounding the cost of drug research and leading the class to tie together ideas presented by different groups.

Do: Students will be assigned financially successful drugs to research. They will gather an electronic profile of the drug that includes the name of the manufacturer, the date the drug became available for prescription, the condition it is used to treat, a video advertisement for the drug, and the retail price for a typical prescription for the drug. Students will upload this profile to Canvas for assessment.

Day 2
Essential vocabulary: Clinical trials, phase 1, phase 2, phase 3, phase 4, efficacy, dosage

Materials: Computers with internet access, chart paper, markers

Essential Questions:
1. How are drug trials conducted?
2. What is the purpose of each phase of a drug trial?

Know: A short lecture with a PowerPoint will be given by the teacher to provide an overview of preclinical and clinical trials.

Understand: The teacher will pull up https://clinicaltrials.gov/ct2/show/NCT02119819 and lead the students through using the U.S. National Library of Medicine site. As a class, the teacher and students will use the information provided on the site to answer the following questions:
1. What condition is the drug being tested supposed to treat?
2. What is the name (or names) of the drug being tested?
3. What phase is this trial?
4. What is the stated purpose of the trial?
5. What is this drug supposed to do in cells? How is it supposed to help?
6. What are the patient requirements for participating in the study?

The students will then be directed to clinicaltrials.gov and be asked to find a phase 2 and phase 3 trial for new drugs to be used in type 2 diabetes. Students are to answer the same five questions for their "hits".

Do: Each student will use chart paper and markers to make an advertisement for one of the trials that they researched. They will use the answers to the research questions they were given to construct an informative, but attractive poster. These will be displayed in the hallway outside the classroom.

Assessment: The following day, students will put finishing touches on their posters and hang them in the hallway. Students will anonymously be assigned posters to look at and be given post-it notes. They must write one question for the author of the poster, and give one piece of positive feedback concerning the information provided by the author. Each person will respond the questions left for them on a separate sheet of paper. This will be submitted to the teacher. The teacher will also evaluate each student poster.

Day 3
Essential vocabulary: independent variable, dependent variable, control, dosage, efficacy, lethal

Materials: paper cups, radish seeds, colored water, soil, fertilizer

Know & Understand: Students will review the phases of a clinical trial and older information on experimental design. Students will be told that they are to set up a mock "phase 2" trial to test the safety, efficacy, and dosage of a fertilizer on radish seeds. They will research the effect of nitrogen based fertilizers on plants and answer slightly altered versions of the questions they answered in the previous lesson:

1. What effect is nitrogen based fertilizer supposed to have on plants?
2. What is the stated purpose of the trial of this phase 2 trial?
3. What is this fertilizer supposed to do in plant cells? How is it supposed to work to encourage growth?
4. What types of controls should be used in this study?

Do: Students will be given some parameters, but then they will work in groups of three or four to fill out an experimental design sheet. The stated problem will be, "Does fertilizer dosage have an effect on the rate of radish seedling growth?" Students will choose variables and controls and design data tables. Students will submit their experimental design for approval. They will make adjustments based on feedback. They will then obtain the needed materials and set up their test groups. Students will carry out their self-determined protocol, and make observations and record measurements over the next two weeks. Students will use the data they collect to construct graphs. They will analyze which of their doses were effective, and which were lethal.
Assessment: Students will write a modified laboratory report of their experiment. They will address how their tests with the fertilizer mirrors aspects of a phase 2 drug trial. They will propose further tests that would be appropriate if their experiment were to move into a mock "phase 3" trial.

Conclusion

Project Lead the Way has a fairly rigid curriculum and pacing guide, so it can be challenging to find class time to fit in extra material like that proposed in this curriculum unit. However, the typical student in these classes is very focused on a career as a medical professional. I feel that medical research and particularly drug development is not adequately addressed in the PLTW curriculum, and prescription medication is going to be a bit part of their future professional practices. It is important that students understand what drugs do, and how they are brought to market for patient care. This curriculum unit will hopefully fill in this gap in the subject matter, and enrich the background knowledge that of my students, so that they can go into their professional training a little bit ahead of the curve on the ins and outs of pharmaceutical development.

Appendix 1—Implementing Teaching Standards

National Science Education Standards

Standard C: Life Science
As a result of activities in grades 9-12, all students should develop an understanding of the cell: cells have particular structures that underlie their functions, and cell functions are regulated.

Standard F: Science in Personal and Social Perspectives
As a result of activities in grades 9-12, all students should develop understanding of personal and community health, including that the severity of disease symptoms is dependent on many factors, such as human resistance and the virulence of the disease-producing organism, and that personal choice concerning fitness and health involves multiple factors.

National Health Care Cluster Foundation Standards

Accountability Criteria 1.2: Diseases and Disorders
Describe common diseases and disorders of each body system (prevention, pathology, diagnosis, treatment).

Accountability Criteria 1.3: Medical Mathematics
Analyze diagrams, charts, graphs, and tables to interpret healthcare results

Next Generation Science Standards

HS.PS2.6 - Motion and Stability: Forces and Interactions
Communicate scientific and technical information about why the molecular-level structure is important in the functioning of designed materials.

HS.LS1.2 - From Molecules to Organisms: Structures and Processes
Develop and use a model to illustrate the hierarchical organization of interacting systems that provide specific functions within multicellular organisms.

DCI - LS1.A - From Molecules to Organisms: Structures and Processes - Structure and Function
Systems of specialized cells within organisms help them perform the essential functions of life. (HS-LS1-1)

Appendix 2—Teacher Resources

Lesson 1:

https://www.webmd.com/diabetes/tc/diabetes-differences-between-type-1-and-2-topic-overview
An overview of the difference between type 1 and type 2 diabetes.

http://www.mayoclinic.org/diseases-conditions/type-1-diabetes/symptoms-causes/dxc-20340979
Article directly addressing type 1 diabetes

https://medlineplus.gov/ency/article/003466.htm
Explains how a glucose tolerance test is performed.

Lesson 2:

https://wa.kaiserpermanente.org/healthAndWellness/index.jhtml?item=/common/healthAndWellness/conditions/diabetes/insulinProcess.html
A very simple explanation of the insulin-glucose connection.

http://sphweb.bumc.bu.edu/otlt/MPH-Modules/PH/Exercise/Exercise6.html
Explains link between exercise and GLUT4 expression.

http://pdb101.rcsb.org/motm/182
An excellent explanation of insulin receptors and their role in the signal transduction cascade.

Lesson 3:

https://nieonline.com/tbtimes/downloads/CCSS_reading.pdf
A PDF published by “Newspaper in Education”. It gives detailed information on how to conduct “close reading” in the classroom.

https://clinicaltrials.gov/ct2/show/NCT02119819
A study taken from the clinicaltrials.gov website that can be used for class discussion and direction when introducing lesson 3. Note: Exenatide is derived from lizard venom!

https://www.fda.gov/downloads/drugs/resourcesforyou/consumers/ucm284393.pdf
“Drug Approval Process.” U.S. Food & Drug Administration, U.S. Food & Drug Administration.
Flier for consumers that illustrates the drug approval process.

Appendix 3—Student Resources

Lesson 1: Diagnosing Diabetes
Create-A-Graph: Students will use this site to make graphs from data collected in glucose tolerance test: https://nces.ed.gov/nceskids/createagraph/

Lesson 2: The Physiology of Diabetes

http://kidshealth.org/kid/videos/indiabetes_vd.html (There are 4 short videos at this site: scroll down to see all of them.) These are some animations that describe the insulin-glucose connection simply.

https://www.abpischools.org.uk/topic/diabetes-16plus/10?_sm_au_=iVVMQMRSR9JDDZ05
This is an interactive quiz that allows students to review the concepts of diabetes on their own.

Lesson 3: Developing Treatments for Diabetes

Students will be introduced to the lesson #3 by reading this article on drug prices:
Emanuel, Ezekiel J. "The Solution to Drug Prices." The New York Times, The New York Times, 9 Sept. 2015, www.nytimes.com/2015/09/09/opinion/the-solution-to-drug-prices.html?_r=0 .

Center for Drug Evaluation and Research. "How Drugs are Developed and Approved." U S Food and Drug Administration Home Page, Center for Drug Evaluation and Research, www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm. From Fish to Pharmacies: A story of drug development

"Drug Approval Process." U.S. Food & Drug Administration, U.S. Food & Drug Administration, www.fda.gov/downloads/drugs/resourcesforyou/consumers/ucm284393.pdf . Flier for consumers that illustrates the drug approval process.

Students will research current clinical studies of type 2 diabetes using the NIH NLM database:
"Search of: Recruiting Studies." ClinicalTrials.gov, NIH U.S. National Library of Medicine, https://clinicaltrials.gov/beta/. For use in student research of current clinical studies.

Students will do a close reading of the introduction of this scholarly article:
Koistinen, Heikki A., et al. "5-Amino-Imidazole Carboxamide Riboside Increases Glucose Transport and Cell-Surface GLUT4 Content in Skeletal Muscle From Subjects With Type 2 Diabetes." *Diabetes*, American Diabetes Association, 1 May 2003, diabetes.diabetesjournals.org/content/52/5/1066.

A Study to Compare a New Drug for Type 2 Diabetes to Placebo and to a Treatment Already Available for Type 2 Diabetes - Full Text View. (n.d.). Retrieved October 05, 2017, from https://clinicaltrials.gov/ct2/show/NCT02119819

Bibliography

"National Diabetes Statistics Report, 2017." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 17 July 2017, www.cdc.gov/diabetes/data/statistics/statistics-report.html.
Provides statistics related to the prevalence of diabetes in the U.S., risk factors, complications, deaths and financial impact.

American Diabetes Association. (2013, April 01). Economic Costs of Diabetes in the U.S. in 2012. Retrieved October 05, 2017, from http://care.diabetesjournals.org/content/36/4/1033
Study that estimates the financial impact of diabetes in 2012.

Type 1 Diabetes. (2017, August 07). Retrieved October 05, 2017, from http://www.mayoclinic.org/diseases-conditions/type-1-diabetes/symptoms-causes/dxc-20340979
Article for a general audience that describes type 1 diabetes causes, risk factors and complications. Provides an explanation of the roles of insulin and glucose.

Center for Drug Evaluation and Research. "Drug Approvals and Databases - Drugs@FDA Glossary of Terms." U S Food and Drug Administration Home Page, Center for Drug Evaluation and Research, www.fda.gov/drugs/informationondrugs/ucm079436.htm#D. Defines important terms necessary for the curriculum unit.

Huang, S., & Czech, M. (2007, April 03). The GLUT4 Glucose Transporter. Retrieved December 08, 2017, from http://www.sciencedirect.com/science/article/pii/S1550413107000678
Provides a technical explanation of the interaction of insulin with insulin receptors, the signal transduction cascade, and the translocation of GLUT4 proteins.

A Study to Compare a New Drug for Type 2 Diabetes to Placebo and to a Treatment Already Available for Type 2 Diabetes - Full Text View. (n.d.). Retrieved October 05, 2017, from https://clinicaltrials.gov/ct2/show/NCT02119819. A good example of the type of study that students are to search for and analyze for lesson 3, day 2.

Emanuel, Ezekiel J. "The Solution to Drug Prices." The New York Times, The New York Times, 9 Sept. 2015, www.nytimes.com/2015/09/09/opinion/the-solution-to-drug-prices.html?_r=0 . Fairly recent newspaper article that outlines how the cost of drug research is passed on to the consumer. Used to introduce the unit on drug research to students.

"Clinical Trial Phases." *CERN Foundation Ependymoma Cancer Research*, Collaborative Ependymoma Research Network, www.cern-foundation.org/education/clinical-trials/clinical-trial-phases. Web page written for general audience that provides an overview of what occurs in the different phases of a clinical trial, and the time frame and sample population for each.

Center for Drug Evaluation and Research. "How Drugs are Developed and Approved." U S Food and Drug Administration Home Page, Center for Drug Evaluation and Research, www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/defau

lt.htm. Introduction to the guidelines provided to make sure drugs that make it to market are effective and safe. The role of CDER is explained. A sample case study is used to make the steps and protocols clear.

Doogue, Matthew P., and Thomas M. Polasek. “The ABCD of clinical pharmacokinetics.” Therapeutic Advances in Drug Safety, SAGE Publications, Feb. 2013, www.ncbi.nlm.nih.gov/pmc/articles/PMC4110820/ . Explains the history of ADME: absorption, distribution, metabolism and excretion, and how modern pharmacokinetics has incorporated this older concept into the ABCD: Absorption, bioavailability, clearance and distribution. Each of these processes is explained.

Amanda, et al. “Pharmacokinetics Basics- Absorption, Distribution, Metabolism and Excretion | Notes.” PharmaXChange.info, 10 Apr. 2011, pharmaxchange.info/press/2011/04/pharmacokinetics-basics-absorption-distribution-metabolism-and-excretion/. A technical explanation of ADME. This reading is directed toward chemists and others with science background.

Stevens, Erland. “Meeting #8: Absorption and Bioavailability.” CTI: Chemical Interactions in the Body, 5 October, 2017. Davidson, NC, Davidson College. Handout, notes, and websites used for part 1 of a seminar on ADME/ABCD.

Stevens, Erland. “Meeting #9: Metabolism, Distribution and Excretion.” CTI: Chemical Interactions in the Body, 10 Oct. 2017, Davidson, NC, Davidson College. Handout, notes, and websites used for part 2 of a seminar on ADME/ABCD.

Kolterman, O. G., Gray, R. S., Griffin, J., Burstein, P., Insel, J., Scarlett, J. A., & Olefsky, J. M. (1981, October). Receptor and postreceptor defects contribute to the insulin resistance in noninsulin-dependent diabetes mellitus. Retrieved December 08, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC370882/. An older scholarly article in which groups of obese and non-obese, impaired glucose tolerant and type 2 diabetic patients were studied to determine the dose-response relationship between serum insulin levels and the rate glucose clearance from blood. It was determined that multiple factors were at play in both groups.

Prediabetes & Insulin Resistance. (2009, August 01). Retrieved December 08, 2017, from https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/prediabetes-insulin-resistance. Provides an explanation of insulin and its role in regulating blood glucose levels. Useful in understanding the mechanisms of blood glucose homeostasis, and why insulin therapy is necessary in some diabetics but not others.

2005, JACKIE ROSENHEK [illegible] September. “Doctor's l
Review | Liquid Gold, 8 Dec. 2017, www.doctorsreview.com/history/sep05_history/. A fun look at the history of uroscopy. Describes the role of urine study in medical knowledge.

End Notes

[1] Carroll, Lewis et al *The Annotated Alice: Alice's Adventures in Wonderland and Through the Looking Glass*. Wings Books, 1998.

[2] See Martin Gardner's musings on the stereochemistry of milk in note 6 of *The Annotated Alice: Alice's Adventures in Wonderland and Through the Looking Glass*. Wings Books, 1998.

[3] Project Lead the Way: Our Programs. (n.d.). Retrieved December 08, 2017, from https://www.pltw.org/our-programs

[4] Figures 1 and 2 by Kari Rhoades

[5] According to Doctor's Review "Liquid Gold", English physician Thomas Willis (1621-1675 described the flavor of diabetic urine as "wonderfully sweet as if it were imbued with honey or sugar."

[6] Akt2…appears to control GLUT4 trafficking in adipose and muscle cells as well as mediate insulin signaling to control glucose output in liver. "The GLUT4 Glucose Transporter." Cell Metabolism, Cell Press, 3 Apr. 2007, www.sciencedirect.com/science/article/pii/S1550413107000678 .

[7] https://nces.ed.gov/nceskids/createagraph/

[8] http://kidshealth.org/kid/videos/indiabetes_vd.html

[9] https://www.nytimes.com/2015/09/09/opinion/the-solution-to-drug-prices.html?_r=0

[10] http://www.readingrockets.org/strategies/think-pair-share