



PREGNANCY PROJECT GUIDEBOOK

IGEM 2020: TEAM DNHS

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Acknowledgments

The format and idea for this guidebook was heavily influenced by Team Technion 2017's "Ethic Handbook."

We would also like to thank the past preeclamptic patients and the obstetrician-gynecologist who helped guide us in realizing the importance of the viewpoints we discuss in this guidebook.

Disclaimer

This guidebook is by no means completely authoritative or scientifically factual. Our intent is simply to help guide future iGEM teams in creating their projects based on our personal experiences. If there is any mistake that arises after distribution, we take responsibility and apologize for these errors.

If you have any questions or comments please contact us at

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Introduction

Purpose

The main purpose of this guidebook is to encourage the best ethical values while developing solutions for pregnancy-related projects. When dealing with synthetic biology, there are many concerns to think about such as “maximizing public benefits while minimizing public harm” (Gutmann), constantly looking for any possible risks, and respecting opposing sides when receiving input. Some worries even extend to developing a product that is equitable when accounting for all genders, races and citizens of our society. The importance of these factors is especially amplified when dealing with as sensitive a topic as pregnancy, which is why we felt it was important to share our experiences and advice. Through this guidebook we hope to lead fellow teenagers and young adults to their highest level of success while respecting the significance of core moral/ethical values.

While developing our project we discovered four points of view that are most important to consider when trying to avoid any complications with these ethical concerns. The first point of view we will be discussing is the student point of view. When starting our project we had no idea how to connect with our community or deduce whether our ideas were achievable. Through many trials and errors we were able to create a narrowed list of favorable starting points and in this section we explain the steps that will help guide students toward successfully reaching their goals while dealing with a project in a demographic they are not part of (in our case, pregnant patients). In the second point of view, the patients', we explain the main problems that will arise while putting yourself in a mother's shoes and help guide your thinking about the well being of herself and her baby when deciding your solution. The ideas from this section come directly from the interviews we conducted with preeclamptic patients. Lastly, with the help of interviews with doctors and several literature searches, we go through the point of view of doctors and manufacturers to ensure that every stage of the solution process is covered and ensures the most benefit for everyone.

iGEM

iGEM (International Genetically Engineered Machine) is a synthetic biology research competition in which students in high school and undergraduate colleges from all over the world can display their research projects on any issue. These issues range in topics from environmental problems (such as plastic wastes in oceans- our project from last year) to disease related problems (such as preeclampsia- our project this year). The project requires teams to include lab work that tests various solutions and outreach to the community to see how the solution affects society.

This year our project focuses on developing a viable treatment for preeclampsia. We came across preeclampsia as we were researching common diseases in the early stages of our project. Though we hadn't heard much about it before, we quickly came to realize that to this day, this pregnancy complication still does not have a reliable solution that ensures the safety of both the mother and the fetus. This inspired us especially since preeclampsia continues to affect almost 8% of pregnant women worldwide, which is about 320 million mothers who are likely forced to undergo premature birth. In order to help reduce the number of babies that are introduced into the world with malnutrition, difficulties, or even death, and the number of women who suffer from a dangerous or deadly labor, we felt it was important to be able to create a solution that will aid the mother and consequently the baby. Also, after learning about the limited number of people in our community that knew about this disease, we wanted to be able to spread awareness to be able to ease the stress of those that might be affected in the future.

Our main goal is to prevent the dangerous (yet common) manifestations of preeclampsia in pregnant women, thus eliminating the negative impacts of drugs or induced labor. Preeclampsia is a complication due to the overproduction of the receptor sFlt1 (soluble Fms-like tyrosine kinase 1) in endothelial cells reducing free molecules of the angiogenic factors PLGF (Placental Growth Factor) and VEGF (Vascular Endothelial Growth Factor) and we found the best way to reduce the effect of the receptor would be to stop the translation of its mRNA. In order to do this, we plan to produce an effective siRNA treatment using lentiviral vectors to carry and deliver shRNA to the trophoblast and thus treat preeclampsia at the molecular level. Through this project, we ultimately hope to eliminate the need to pit the health of a mother against that of her child, which doctors are commonly forced to do when they induce early labor to alleviate the symptoms of preeclampsia.

Student Point of View

As high school or college students without many contacts you might be afraid of lacking the necessary input to develop the most successful project. In order to help conduct the necessary outreach we suggest you take the social media approach on platforms we are all familiar with as teenagers. Though this approach may seem unprofessional, in the day and age we are in today, we found this was the best method as it is widely used and easily accessible as well. Even if you may think there isn't a significant presence of the disease your project is focused on, social media has the tools that will lead you to the contacts you will need to broaden your perspective. The important thing is, just as you would take great care in drafting out an email that sounds professional and respectful, you must maintain a similar tone when reaching out to people on social media (email/message examples are on page 7). For our project, when searching up hashtags like "#preeclampsia" and "#preeclampsiaawareness," we found many patients who were spreading awareness and willing to answer interview questions about their experiences. Since doctors also don't disclose their personal information such as email online, we were also able to search up the hashtag "#OBGYN" and even found obstetricians willing to answer questions that helped develop our treatment idea. Through this approach, we were able to conduct interviews with 7 past preeclampsia patients and an obstetrician (their input further discussed in later sections). As you can see, social media is a very viable platform to spread and receive awareness to create a connection between your community and your project, but during this process it is also very important to take account of the privacy of the patient and their information. In our project we made sure to keep our patient's names anonymous after consulting them about using their feedback and input during our interviews.

After conducting interviews in an ethical manner that respects the patient's privacy and spreading awareness through infographic posters, we also spread google form surveys that served as anchors to help us grow and further develop our project. During our project this year, we conducted two surveys. We gave our first survey to those we interviewed to receive feedback on our approach being high school students and our second survey was to our general community to find out how knowledgeable they were about preeclampsia/synthetic biology. Creating these surveys will be a vital aspect for your project since they act as direct answers showing whether you are going on the right path. By creating a youtube and instagram account, we were also ultimately able to reach and educate a more widespread audience. We created videos on topics ranging from DNA Transformation to our project and created infographics that spread awareness about preeclampsia as a disease in general. With this approach, we were able maintain attention from our audience while providing thorough information on the topic.

Message & Email Examples

Instagram Message (patients):

Hi Ms. _____,

We are part of Del Norte High School's iGEM team. iGEM (international Genetically Engineered Machine) is a synthetic biology research competition in which teams from all over the world can display their research projects on any issue. After much research we decided to do our project on preeclampsia, as we wanted to explore treatments to a disease that is common and unfortunately dangerous but still without a reliable treatment. We found your account while looking at hashtags used by people who have experienced and are spreading awareness about preeclampsia and your account/post caught our eye.

Please let us know if you would be interested and comfortable with answering a few questions about your journey through preeclampsia.

Thank you!

Instagram Message (doctors):

Hi Dr. _____,

We are part of Del Norte High School's iGEM team. iGEM (international Genetically Engineered Machine) is a synthetic biology research competition in which teams from all over the world can display their research projects on any issue. After much research we decided to do our project on preeclampsia, as we wanted to explore treatments to a disease that is common and unfortunately dangerous but still without a reliable treatment. We found your account while looking at hashtags of gynecologists/OBGYNS and your account/post caught our eye.

Please let us know if you would be interested and comfortable with answering a few questions about your experience treating patients. Our email is delnorteigem@gmail.com and feel free to contact us there if that is a better source of communication. Also, if you know any doctors that specifically treat preeclampsia we would love to contact them as well.

Thank you!

Email to doctors:

Dear Dr. _____,

We are part of Del Norte High School's iGEM team and are looking for some input and feedback on your experience working with patients. iGEM (International Genetically Engineered Machine) is a synthetic biology research competition in which teams from all over the world can display their research projects on any issue. The project requires teams to include lab work that tests various solutions and outreach to the community to see how the solution affects society. After doing much research on diseases, we learned about preeclampsia and wanted to test out possible solutions. As such, we are hoping to use synthetic biology in our project to find an siRNA sequence that would inhibit SLFT-1 to see overall improvements in preeclampsia. Due to the ongoing pandemic, we are unable to work in a lab, but will be testing this method with online software that will allow us to model our idea.

Thank you for taking the time to read our project idea, and Please let us know if you would be interested and comfortable with answering a few questions about your experiences with helping preeclamptic patients.

Thank you,
DNHS iGEM

Patient Point of View

Timing

Following the hippocratic oath that protects the patient's privacy while conducting interviews of past patients with the disease you are targeting, is a vital resource that is necessary for you to reach your highest potential. As we mentioned before, we contacted patients through instagram and received some important critique that you should consider as well. Most importantly, a trend between all the patients showed that there wasn't a common diagnosis period for preeclamptic patients. This meant that pregnant women could get preeclampsia during any term of their pregnancy which meant our delivery method would need to be flexible enough to adapt to these differences. The patients that were diagnosed just 2 days before their delivery would need a faster working treatment whereas those that were diagnosed several months prior could take several doses throughout their remaining pregnancy. For this reason it is very important to research several different literature that discuss the diagnosis period of your target disease and the time period of treatment effectiveness after exposure by looking at experiments with similar methods. After this research you will need to figure out a correlation between both to create a dosage plan that ensures the best results and effectiveness for all cases of pregnancies with that particular disease.

While finding literature to support our project, we found an experiment researchers performed on preeclamptic mice. They found the dosage of 20 mg/kg siRNA injected into 15-day pregnant mice would have 40% lower sFlt mRNA by day 19. Based on these experiments, we hypothesize that the optimal siRNA dosage for humans is around 20 mg/kg and depending on diagnosis period we will either need to increase or decrease their dosage. We would base this dosage plan on our furthered knowledge that siRNA knockdown effects are likely to be observed 4 days after injection and human pregnancy is much longer than mice, which would mean multiple doses may be needed for every one dose used on the mice.

Effects

During our interviews, when we asked the patient if they would have used our Preeclampsia siRNA treatment when they were diagnosed, everyone of them rightfully stated they couldn't give a definite answer unless it was proven to be safe for the baby and themselves through multiple clinical trials and approved by the FDA. This was not a shock to us but made us realize the prominent importance the effects of this treatment holds for the patients. For this reason, while developing your project, taking into account every possible effect of your treatment should be your utmost priority.

All possible effects that could develop during many pregnancy related diseases can be categorized as either being long term or short term issues involving the mother or the baby. For preeclampsia, after learning more about postpartum preeclampsia (a facet of the condition that is often overlooked), we had to discuss the possibilities of our treatment having a longer term effect that would aid with resolving problems after giving birth. But most importantly, like every other pregnancy-related disease, we had to consider the short term effect of our shRNA treatment damaging the mother's body (discussed in more detail in the next section) or the fetus. When thinking about the baby, you would also need to think about their nutrient supply from the fallopian tube, which cannot be damaged or affected under any circumstance and other sudden consequences that might arise. When looking further into the baby's future, it is also important to consider any possible genetic or cellular changes that might come up after they are born.

Doctor Point of View

When thinking about pregnancy, obstetricians and gynecologists come to mind. In order to create the most effective treatment that one of these doctors would promote and use, you not only need to think about stopping the root cause of the disease you are focusing on, but also maintaining the stability created by multiple factors in one's body. The main concepts to contemplate are the practicality of your design and its mode of reaching your target cell without disturbing other cellular processes.

While developing our project, we didn't realize the importance of these concepts until an obstetrician pointed out specific complications that might arise. She discussed the importance of creating an shRNA sequence that is specifically complementary to the target sFlt1 mRNA and no other strands in the body since the shRNA could easily mistake a similar sequence and ultimately block its translation. This would be highly dangerous due to the interconnection between all the systems and cells within our bodies, which would mean a small disturbance within one cell could cause a malfunction throughout the body. After discussing our idea with her, we also realized the strong impact of an shRNA treatment since it could completely eliminate the presence of all sFlt1 receptors. This would harm the body by affecting angiogenesis (the development of blood vessels). In order to prevent this we had to develop the concept of using our treatment at different concentrations and doses depending on the severity of the pregnancy.

That's why it is important to keep in mind the various potential effects of a treatment created by synthetic biology that might serve your purpose in reversing/treating a harmful condition, but possibly harm other parts of the body that carry out critical functions.

Production Point of View

The first challenge to consider when implementing your treatment is its financial cost. This includes both the cost to develop the therapy and the cost to receive treatment. Gene therapy can be very expensive to develop and test in clinical trials. Furthermore, these procedures must be approved by the FDA (Food and Drug Administration in the U.S.), which is approving an incredible small fraction of gene therapy treatments each year. This expense of money and time is why current siRNA treatments cost around \$400,000 to \$500,000 a year for patients. Due to this reason, it is very important to have researched and gone through multiple literature searches in which you have found the production, testing, and overall costs of similar treatments to estimate and foresee the future of your treatment.

Assuming the treatment is approved by the FDA, the next challenge to consider is competition and the resulting benefits/risks for different demographics in society due to your treatment. Just as inexpensive, conventional drugs today are sold by multiple companies competing for customers, there is a very high chance there is a rival factor against your treatment that you will need to consider. In our project, there are currently no direct treatments for preeclampsia, but rather drugs which treat side effects such as high blood pressure, which arose as opposing factors we had to consider. But, since our procedure would not be in direct competition with any other treatment, we would be able to save many lives in the future by targeting the root cause of preeclampsia, sFlt1, rather than the symptoms like the drugs currently do. For this reason, in order to avoid creating competition for yourself, it is important to develop your treatment after looking at current methods and targeting a cause of the disease that wasn't targeted before, so that you have a novel treatment that may be beneficial for a portion of your targeted demographic. Though the main purpose of your treatments is to aid the recipient, it is also important to take time and consider others who might also be affected, such as rival companies. This is especially necessary to uphold as an ethical value to prevent a great amount of harm to any other established party in your community due to your solution.

Sources

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