Science Fair Logbook

December 6th, 2023 - Discussed possible research topics with coordinator, began to research gain of function research

Gain of function research is a highly effective and efficient type of research used by scientists to modify, and thus better understand dangerous pathogens, specifically those with the potential to endanger the population on a large scale. This research is seen by certain research groups as a means to prevent epidemics, and even global pandemics. Gain of function research does this through modifying pathogens in order to make them more dangerous in one of a variety of ways, including replication, host range, immune evasion, vaccine resistance, virulence, and/or drug resistance. These traits of a virus all relate to viral transmissibility, or the virus's ability to transmit itself, and survive within a host. Although this may seem like a bad idea at first, the possible benefits of gain of function research have the potential to change our entire world in more than one way. These possibilities include the development of pipeline vaccines and other medical countermeasures, such as medication. Gain of function research, although beneficial to a variety of scientific fields, is also considered incredibly risky, due to the way it is done. In addition, it is considered a dual-use research or concern, meaning that it could potentially be used for good in the medical field, though could also be used against humans, as a biological weapon. Of course, this poses a variety of issues to us as a society, specifically to those already immunocompromised.

December 12th, 2023 - Finished research on GoFR, began CYSF registration process.

The past research done using gain of function research has been plagued with controversy, though it has made important contributions to the scientific community. In the early 2000s, scientists experimented with the H5N1 virus, and were able to create a virus with up to 60% mortality rates, however with limited human to human transmission. This was one of the first instances of gain of function research, and sparked conversations relating to the ethics of the form of research. Despite the fact that these scientists' research with the H5N1 virus opened doors for science, there were later concerns with biosecurity, and even bioterrorism. This then led to debates within the World Health Organization (WHO) and many world governments. This is mainly due to the fact that publication of results of these experiments (specifically those relating to flu types viruses, including H5N1) could lead to the development and use of biological weaponry. The next development in this field involved modifying amino acids to lead to random mutations in DNA. This experiment used ferrets, and these mutations resulted

in changes to their transmissibility phenotype, making the virus more deadly, due to its ability to spread more quickly and efficiently. Both of the experiments (with H5N1 and other flu viruses) fell into the level 3 of biosecurity (out of four). This means that the pathogens involved were not as deadly as certain others, though are still fairly dangerous. The most dangerous pathogens (including viruses like Ebolavirus) are subject to more strict rules regarding experimentation and how they are kept within a laboratory. More biosecurity issues regarding gain of function research led to even further examination. For example, there were various safety issues with anthrax during 2014, when researchers were exposed to it at the Centre for Disease Control and Prevention (CDC), and the American Department of Defense shipped anthrax to multiple diagnostic labs across the United States. Later on, there was pathogenic flu found to be in existence within clinical laboratories, and later smallpox found in the National Institute of Health (NIH). Gain of function research is governed by different bodies, including the World Health Organization and world governments, mainly through policies, such as the one regarding Potential Pandemic Pathogen Care and Oversight (P3CO). In addition, there have been many other incidents related to gain of function research that have led to stricter safety restrictions. One of these such incidents was in 2001, when the virulence of mousepox (mouse variola) was accidentally altered in a lab experiment, causing 100% lethality, even with the use of the vaccine. There was a similar experiment conducted that involved H5N1, with 60% lethality, but low virulence. All of these incidents led to the creation of the P3CO.

December 19th, 2023 - Filled out the Basic Project Information on the CYSF platform.

December 21st, 2023 - Worked on the Ethics and Due Care form on the CYSF platform.

January 3rd, 2024 - Started working on the method and problem section of the CYSF platform

Does gain of function research have the ability to combat illnesses through both new and updated vaccines, as well as other protective technology, while still ensuring the safety of the population?

To ensure that I explore all possible outcomes of the gain of function research that will have to be conducted, I will also be exploring all possible outcomes of gain of function research, as well as the probability of these outcomes. Being that this research is currently very controversial, I will ensure to explore both sides of the issue.

January 22nd, 2024 - Completed the problem and method sections of the CYSF platform, and continued my work on the research section.

Primary Objective - To explore the possibilities of using gain of function research to develop new and improved vaccines and protective measures.

Secondary Objective - To understand and convey the possible risks and benefits associated with gain of function research, as well as the recent controversies surrounding research in the past two decades.

By increasing the use of gain of function research in the development and creation of vaccines and other technology, we will be able to both decrease the impacts of the targeted pathogens and create more effective medical countermeasures.

All of the data I used in my project was obtained from a variety of studies conducted by different parties in various parts of the world. The data used was collected through gain of function research in order to ensure the highest possible accuracy of my results. The other information and data obtained from scientific studies was found through research papers and scientific studies collected on a controlled population. The data spans twenty years, in order to show the evolution of the impacts of various pathogens. The data shown within the studies is used in combination with other data, to provide the most accuracy and precision possible. To interpret the data presented in these scientific papers and studies, I looked for patterns within the data, and used these to apply my background knowledge to the new information. I used studies from more than one source, conducted in a variety of different ways, in order to ensure the correctness and credibility of my information. In addition, I used the various health standards of the American, Canadian, and some European governments to better understand these standards and the limitations of gain of function research, and the threats it may pose to certain demographics specifically.

January 30th, 2024 - Continued my work on the research section of the CYSF platform.

Gain of function research has been used in a variety of ways throughout past decades, though most of them centre on understanding the pathogens, rather than the development of any specific medical countermeasure. However, there has been a major development through gain of function research relating to the angiotensin-converting enzyme 2 (ACE-2) receptor. The ACE-2 receptor is found in the cell membranes of cells in the intestines, kidneys, gallbladder, and the heart. The modification involved modifying the receptors to receive different pathogens. The ACE-2 receptor that has been the subject of many experiments involving gain of function research is a glycoprotein. These

proteins are used as a receptor or "key" that allows other cells to identify it. This makes it incredibly dangerous for a virus to target, as it is also part of cells in the most important organs in the human body, including the heart, and the kidneys.This study was one of the first in a series to determine how close certain novel pathogens are to high transmissibility in mammals. In addition, this research could also be used in the development and testing of vaccines on emerging pathogens and/or variants of pathogens. The use of gain of function research in vaccine testing also allows for stronger countermeasures, including in the case of a possible epidemic. Vaccine testing benefits from the creation of stronger variants of existing pathogens through the use of these stronger vaccines to counteract the possible random mutation of the specific pathogen. Despite this, gain of function research is considered a dual-use research of concern (a DURC), and there have been certain limitations placed on a variety of pathogens, including avian flu, anthrax, botulinum neurotoxin, burkholderia mallei, burkholderia pseudomallei, ebolavirus, foot and mouth disease virus, francisella tubrensis, marburg virus, reconstructed 1918 flu virus, rinderpest virus, toxin-producing clostridium botulinum, variola minor, variola major, and yersinia pestus. As shown in the list above, many of these viruses placed under strict restrictions are those that could potentially cause large outbreaks, meaning that these restrictions allow scientists to safely explore these possibilities while still protecting those not involved in the research. Only one mutation in a pathogen can impact a variety of traits of the pathogen, making random genetic mutations incredibly dangerous for the population, and leaving gain of function research with the crucial role of helping predict what these mutations could cause the virus or pathogen to do. In the past decade, other viruses and pathogens have emerged as very dangerous, including SARS-CoV, SARS-CoV-2, ebolavirus, equine encephalitis (horse flu), anthrax, and avian influenza. In the past, gain of function research has been used to increase host range, transmissibility, pathogenicity, and escaping medical countermeasures. The first experiments involving DURCs were published in the early 2000s, and the H5N1 experiments led to the beginning of a controversy, and led to the pause called for by Barack Obama's administration in 2012. Many of the debates surrounding gain of function research not only relate to the ethics involved, but also to the risks and benefits of the research. The risks involved include biosafety, biosecurity, informational risk, agriculture related risks, and economic risks. However, many scientists believe that the benefits far outweigh the risks. These benefits include gain of scientific knowledge, biosurveillance (using GoFR to prevent bioterrorism), medical countermeasures, and economic benefits. Although researchers can use these risks and benefits to analyze the possible risks of gain of function research, the pathogens that are created as a result of GoFR are still considered genetically modified organisms (GMOs), which have laws placed against them in many countries. In Canada, we have very few laws surrounding GMOs, compared to other countries

including France, Japan, and Mexico. These risks associated with GMOs often impact those least involved and most compromised, meaning that the analysis of risks and benefits is incredibly important to prevent possible biosecurity issues.

February 3rd, 2024 - Continued my work on the research section of the CYSF platform.

Gain of function research has been used in the past to predict possible pandemics and epidemics, and can also be used to modify pathogens capable of causing a pandemic, in order to predict the most dangerous possible natural genetic mutations in viruses and other illness-causing pathogens. Pandemics are hard to classify generally, though scientists have used five steps to describe how a virus is eventually able to become an epidemic, and, from there become a pandemic:

1. Circulation in animals - The virus begins to be transmitted within animals

2. Primary human infection - The virus is transmitted from an animal to a human for the first time (examples include West Nile virus and rabies)

3. Limited human-to-human transmission - The virus is first transmitted from a human to another human (ebolavirus, marburg virus, and monkeypox)

4. Sustained human-to-human transmission - The virus can be transmitted between humans quite easily (influenza and dengue)

5. Exclusive human-to-human transmission - The virus can only be transmitted between humans (HIV, tuberculosis, and smallpox)

Before the virus is transmitted to humans, there is an organism that serves as an intermediate host, transmitting the virus from the origin to a human, allowing for the second stage of a pandemic to occur. Because of the fact that this has been shown to occur naturally, scientists are beginning to use gain of function research to both improve existing vaccines, and continue development on pipeline vaccines (vaccines currently in development but not yet fully approved for use by humans).

February 12th, 2024 - Continued my work on the research section of the CYSF platform.

Vaccines currently fully developed include countermeasures for:

- Influenza

- Varicella
- Human papillomavirus infection (HPV)
- Measles, Mumps, and rubella
- Yellow fever
- Malaria
- Pertussis
- Tetanus
- Hepatitis
- Polio
- Rota virus
- Japanese encephalitis
- Tick-borne encephalitis
- Typhoid
- Diphtheria
- Cholera
- Dengue
- COVID-19

Currently developing vaccines include:

- Escherichia Coli
- Chikungunya
- Herpes
- Human immunodeficiency virus (HIV)
- Gonorrhea

Although COVID-19 is a relatively new pathogen, it has still had far reaching impacts, specifically those related to other related pathogens. The below table showcases the relative lethality and other information surrounding viruses related to COVID-19.

MERS (Middle East Respiratory Syndrome)	35% lethality, low transmissibility, only prevalent in the Middle East and South Korea
SARS (Sudden Acute Respiratory Syndrome)	7.8% lethality, has the ability to recognize ACE-2 receptors
COVID-19	1.4% lethality, can recognize ACE-2 receptors

Despite the fact that COVID-19 has a relatively low lethality rate, there was an experiment conducted following the pandemic that modified a gene in the omega strain to alter the lethality, increasing it to 80%. COVID-19 is a single strand of RNA made up of

29 600 nucleotides. Modifying only one of these could lead to a significantly higher lethality rate, or higher virulence.

February 25th, 2024 - Continued work on research.

There have previously been breakthroughs relating to SARS, mainly to do with the mechanisms of both viruses and pandemics. In the cases of COVID-19 and SARS, bats served as the intermediate host, and played a large role in the transmission of both viruses. In the early 2000s, there were lab-related issues involving West Nile virus, dengue fever, and, most importantly, SARS. In China, there were issues in a mineshaft near a laboratory that was conducting research on SARS. When this virus escaped the laboratory through bats that had been living in the mineshaft, both had a mortality rate of around 50%, and quickly evolved into pneumonia, after its initial infection. This shows the importance of the intermediate host (specifically bats) in the spreading of pathogens. Of course, this was another one of the incidents that caused more strict laboratory and safety restrictions in general.

March 4th, 2024 - Finished my research.

The previous uses of gain of function research will have an impact on the creation and development of medical technologies in the future, specifically target vaccines and countermeasures designed for a specific pathogen. These vaccines and countermeasures can specifically target different viruses whose vaccines are currently under development, including HIV, as well as viruses whose vaccines have not yet been developed, including ebolavirus. The reasons for these vaccines being underdeveloped include a variety of scientific issues, but also issues involving the fact that many dangerous viruses, including ebola, are not prevalent in the first world countries that have the ability to fund the research needed to develop such vaccines, and even stronger medicines. This also poses issues in the economy of third world countries, being that many of the countries affected by viruses such as ebola are heavily reliant on foreign aid for their needs, meaning that, should a vaccine be developed, the people who need it most may not have access to it. However, there are also other people impacted by rarely researched viruses, including here in Canada. Many of the scientific breakthroughs involving gain of function research discussed above can be applied to other viruses. Despite the differing nature of the viruses discussed above, such as COVID-19, we can use the previous discoveries to apply what we currently know about well-known viruses to discover similar things about other, less prevalent viruses. Of course, this would require the use of similar methods (including gain of function research) with potentially more dangerous

viruses (ebolavirus requires the highest level safety precautions). Despite the possible risks, there are restrictions in place for gain of function research, meaning that this research can be used for the good of many people, and ensure that another pandemic is not a likely possibility. The earlier breakthroughs mainly relate to SARS, MERS, as well as other possible variants of COVID-19. Although the recent pandemic is under control, and COVID-19 is becoming less of a concern, there is still a possibility of a natural genetic mutation that would infect, and possibly kill, more people than the original variant. A good example of why and how this is possible is the newest variant of COVID-19, known as JN.1. This strain is a result of more than one genetic mutation of the virus, and went from causing only 1% of COVID-19 cases to now being estimated to cause 86% of current cases. JN.1 differs from other COVID-19 sublineages in the way that one of its natural random genetic mutations was to the n-protein (the main body protein of COVID-19). It also mutated on its spike protein, which is the protein that helps the virus bind to and infect cells. This is the protein that often houses the mutation that causes a virus to naturally mutate. All RNA based viruses naturally mutate, including COVID-19 and SARS, and COVID has a relatively low mutation rate. However, the JN.1 mutation increased the transmissibility by a large amount, and caused an increase in infection rates, as well as an increase in immune evasion. Gain of function research can allow for researchers to predict other possible variants of COVID-19, as well as mutations of SARS that may lead to the outbreak of another virus (the way COVID-19 was originally created). The use of gain of function research for this use could predict pandemics, as well as develop new, protein-based vaccines for viruses. All of this information is incredibly important, as it will allow for us to plan for and even prevent future pandemics. Specifically, the research that can be applied to COVID-19 and its different strains and variants. This can not only allow us to prevent pandemics, but also better understand the nature of viruses in general (there is currently very little information known on viruses in general). Although our society has come a long way in the past few years in terms of medical technology, there is still a need for new and improved technology to protect and cure people from viruses, and improve our vaccines and medicines in general.

March 7th, 2024 - Completed the data section of the CYSF platform and worked on the creation of my presentation

March 12th, 2024 - Finished my script for my presentation, and edited my project.

March 13th, 2024 - Recorded my presentation.