Canada Gairdner Awards 2021 Laureates Education Materials

(Artwork) Armin Mortazavi: (Writers) Brenna Hay, Sarah Laframboise, David Ng, Farah Qaiser, Zahra Sepehri, Rhonda Thygesen, and Nicole Wang.

TABLE OF CONTENTS

In collaboration with CSMB and the Michael Smith Laboratories at UBC, these materials were produce to provide a series of articles, comics, and accompanying lesson ideas to celebrate the science of a selection of this year's Canada Gairdner Awardees. We invite you to view and share these documents widely, as they highlight the impact science has in our lives and our understanding of the world.

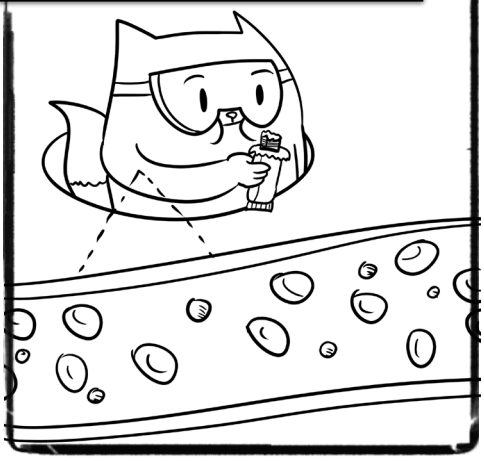
For more information about the Gairdner Foundation (as well as links to supplementary video content), please visit https://gairdner.org

For more information about the Canadian Society for Molecular Biosciences, please visit https://csmb-scbm.ca/

The Molecular Elements of Diabetes

1

Your body uses chemical messengers, called hormones, to maintain healthy levels of sugar in your blood.



2

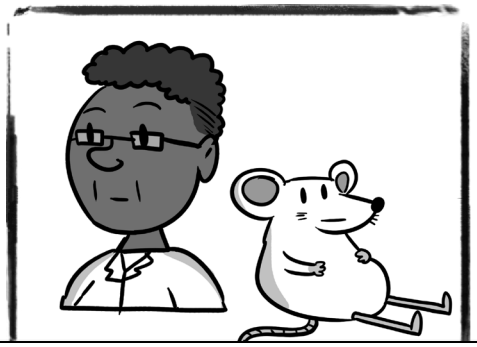
Insulin stimulates the cells in your body to take up glucose, so that it can be used as fuel. Glucagon does the opposite: it helps the body move glucose out of cells, raising the level of sugar in the blood.

3

But how does your body control insulin and glucagon to maintain healthy levels of sugar?

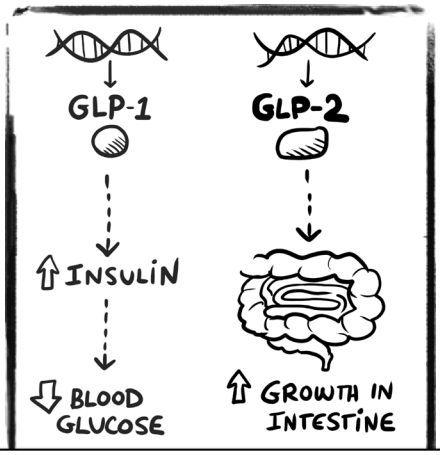
This is what Drs Daniel Drucker, Joel Habener and Jens Holst have been investigating for over 30 years.

4



Using experiments in rodents and humans, the three scientists characterized two new gut hormones, called glucagon-like peptides (GLPs): GLP-1 and GLP-2.

5



They found that GLP-1 stimulates the release of insulin, helping normalize high levels of glucose, while GLP-2 acts as a gut growth factor and stimulates growth in the intestine

This led to major advances in the treatment of Type 2 diabetes, obesity and intestinal disorders. In recognition of their work, Drucker, Habener and Holst were awarded a Canada Gairdner International Award in 2021.

6

Art by Armin Mortazavi and text by Farah Qaiser. October 2021

The Molecular Elements of Diabetes

The characterization of glucagon-like peptides, has lead to major advances in the treatment of Type 2 diabetes, obesity and intestinal disorders.

Written by Farah Qaiser
Art by Armin Mortazavi

October 2021

Every time you have a snack, your body's digestive system leaps into action.

Digestion begins in your mouth, where your teeth, and the enzymes present in your saliva, break food down into smaller pieces. Next, food enters the esophagus, and is pushed towards your stomach, small intestine, and large intestine to undergo additional digestion. For example, your stomach's enzymes and acidic environment will digest proteins, while the large intestine will reabsorb water and process any waste. Various organs, including your liver, pancreas and gallbladder, will help with food digestion by releasing different enzymes and secretions, such as bile (a digestive juice which breaks down fats).

This is simply a snapshot of the complex process of digestion! Your body coordinates all of the different players involved using chemical messengers, called **hormones**. Hormones travel to different parts of the body through the bloodstream, and tell cells what to do. They control many of the body's important processes, including growth, metabolism and development.

The human body makes around 50 different hormones, including **insulin** and **glucagon**. Both insulin and glucagon are produced by cells in the pancreas, and are critical for digestion. Insulin stimulates the cells in your body to take up **glucose** (a type of sugar) from the bloodstream, so that it can be used as fuel. This results in a lower amount of glucose in your blood. Glucagon does the opposite: it helps the body move glucose out of cells, raising the level of sugar in the bloodstream.

Maintaining optimal levels of insulin and glucagon is critical for your health. For example, **diabetes** is the disease which occurs if your body can't make enough insulin (**Type I Diabetes**) or isn't able to use insulin well (**Type II Diabetes**). Without enough insulin, there will be too much sugar in

your blood. This can cause damage to nerves, organs and blood vessels, leading to complications, such as kidney and eye disease.

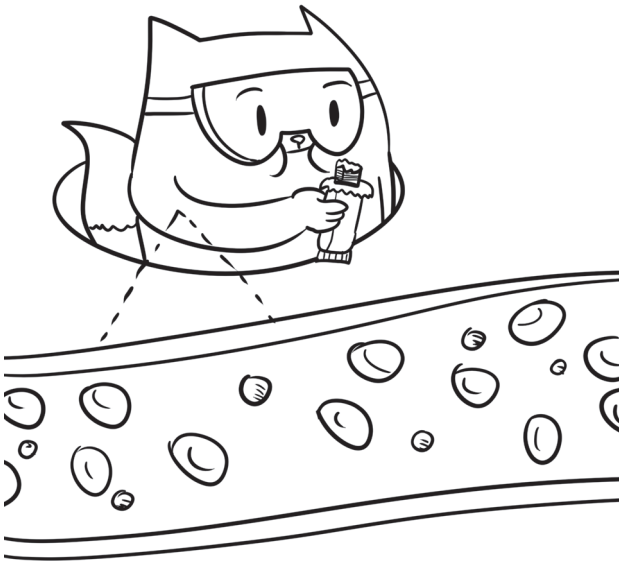
But how does your body control insulin and glucagon to maintain healthy levels of sugar?

This is the question that Drs Daniel Drucker, Joel Habener and Jens Holst have been investigating for over 30 years.

Exploring mysteries in the gut

In the 1970s, Holst was a surgical resident in Denmark. He curiously observed that after meals, many of his intestinal surgery patients were experiencing spikes in insulin, resulting in a drop in blood sugar. This was a clue: perhaps there was another molecule involved in regulating the levels of blood sugar, in addition to glucagon and insulin.

"That was interesting to me," says Holst. "It seemed to involve the gut."



At the same time, researchers in Habener's laboratory used pancreatic cells from anglerfish to show that glucagon – the hormone which helps the body move glucose out of cells – is produced from a larger precursor hormone, called **proglucagon**. Habener's laboratory found that proglucagon contained the sequences to produce glucagon, as well as two previously unknown hormones related to glucagon, called **glucagon-like peptides** (GLPs): **GLP-1** and **GLP-2**. In essence, proglucagon is broken down to three separate hormones: glucagon, GLP-1 and GLP-2.

But what did these mystery glucagon-like molecules do?

In the summer of 1984, Drucker joined as a research fellow in Habener's laboratory in Boston, Massachusetts. Drucker had completed medical school and hoped to pursue research related to the thyroid gland, but was instead assigned to work on the proglucagon gene, where he investigated how proglucagon was processed, and how GLP-1 acted on insulin-producing cells.

"I was pretty unhappy and feeling sorry for myself – that my dream of thyroid research had been sort of stopped in its tracks, but we know how this story ends. It was serendipitously an amazing stroke of luck for me," says Drucker, recalling the early days of his research.

A snapshot of GLP-1's many functions

Through different experiments in rats, pigs and human cells, Holst, Drucker and Habener showed that when food is ingested, GLP-1 is released into the bloodstream, stimulating the release of insulin, and suppressing glucagon. Additional studies showed that GLP-1 injections could help normalize high levels of glucose in patients with Type II diabetes, offering enormous potential for therapeutics.

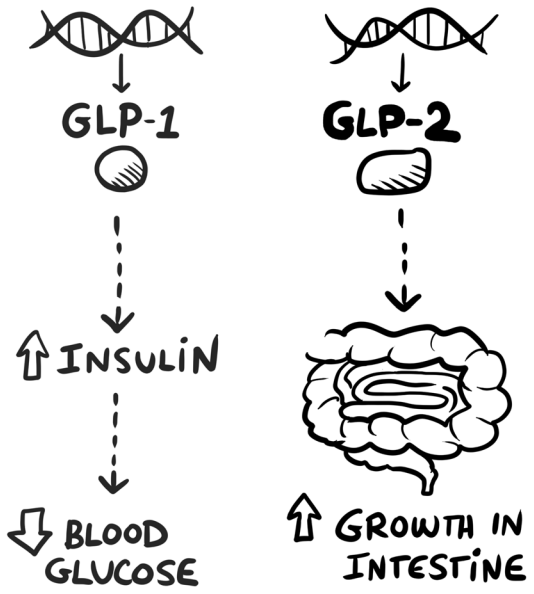
But despite this exciting breakthrough, there was an issue: it only took 1.5 to 2 minutes for GLP-1 levels to be halved in patients with diabetes. This meant that GLP-1 injections were disappointingly ineffective, due to the human body's fast metabolism. Why was GLP-1 being digested so quickly?

Using experiments in pigs, Holst and Dr. Carolyn Deacon found that GLP-1 was broken down by the enzyme dipeptidyl-peptidase-4 (**DPP-4**), and that blocking (**inhibiting**) DPP-4 could completely protect GLP-1. As a result, researchers have developed clinically useful oral DPP-4 inhibitors,

offering new treatments for diabetes. The first DPP4 inhibitor (sitagliptin) was approved to treat Type II diabetes in 2006.

"The amazing thing about these pills is that they basically had no side effects. They didn't even cause low blood sugar. You didn't need to prick your finger to check your blood sugar. That was a huge advance for people," says Drucker.

By better understanding GLP-1, Habener, Drucker and Holst's research also spurred the development of GLP-1 receptor **agonists**, basically molecules which could mimic the action of GLP-1, without having to worry about DPP-4 breaking it down quickly. In 2005, the first GLP-1 receptor agonist, to be used twice daily, was approved for diabetes treatment, and helped prevent the level of blood sugar from rising too high. Today, there are GLP-1 receptor agonists that only need to be used once a week.



Unravelling GLP2's role in digestion

But what about GLP-2 – what does this gut hormone do?

This was what Drucker continued to investigate when he returned to Toronto in 1987. Using experiments in rodents, members of Drucker's laboratory found that GLP-2 acts as a gut growth factor, stimulating intestinal growth and enhancing intestinal function.

These GLP-2 findings in animals were extended to humans with short bowel syndrome, a disorder where fluids are poorly absorbed in the small intestine (usually due to surgical removal of parts of the intestine). In the early 2000s, Holst, Jeppesen and a group of researchers found that when humans with short bowel syndrome received GLP-2 injections twice a day, the patients experienced increased nutrient absorption and weight gain over 35 days.

This critical breakthrough led to the launch of another drug development program, where clinical studies tested the effectiveness of *teduglutide*, a GLP-2 **analogue** (that is, a molecule with a similar structure as GLP-2), as a therapeutic. In 2012, teduglutide was approved for clinical use in the treatment of short bowel syndrome.

Understanding GLPs have led to many medical breakthroughs

This is simply a snapshot: Drucker, Habener and Holst's characterization of GLPs have led to many major advances in the treatment of Type 2 diabetes, obesity and intestinal disorders. In recognition of their work, Drucker, Habener and Holst were awarded a Canada Gairdner International Award in 2021 – the same year which also happens to mark the 100th anniversary of the discovery of insulin. So, what are Drucker, Habener and Holst doing today?

"Actually, I'm still working on exactly the same thing I was working on 30 years ago, because it's been a really cool story and I'm trying to figure out how it works and how to make it better," says Drucker.

He points out that to "make a drug, you don't really have to know how it works. You have to know if it works, and you have to know that it's safe. We know the GLP-1 works really well, and [that] GLP-2 works really well [too]. We know their safety profile thankfully, it looks all good, but the real detail scientifically of how all of these actions

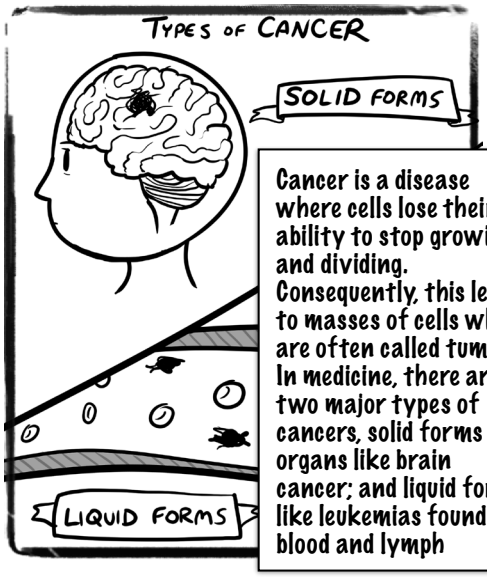
happen, is largely still a mystery."

Similarly, Holst continues to research gut hormones today, especially their role in obesity and intestinal disorders. He has a simple message for budding young scientists.

"Have open eyes, and be curious," says Holst. "Once you get somewhere, find something, stay on it, and continue to work hard. It will pay off."

From the Lab Bench to the Hospital Bed

1



Cancer is a disease where cells lose their ability to stop growing and dividing. Consequently, this leads to masses of cells which are often called tumors. In medicine, there are two major types of cancers, solid forms in organs like brain cancer; and liquid forms like leukemias found in blood and lymph

2

Cancer is a very common disease. In fact, 1 in 2 Canadians will develop cancer in their lifetime, and will need anti-cancer treatments. These treatments have undergone extensive testing so that they can be effective, but many also have unwanted side effects.

3

Many scientists study how treatments work on cancer cells in controlled laboratory settings: We tend to call them "basic research scientists." However, there are also scientists who take these lab discoveries and assess them on the cancer patients themselves. We tend to call these "clinical scientists".

4

Dr. Elizabeth Eisenhauer is a clinical scientist and an expert on how to best evaluate methods used to test treatments. This might include just having great guidelines on which drug candidates are good for testing, as well as strategies and rules on how to test and when to stop testing a drug.

5

For instance, Eisenhauer recognized that not everything needs to be new to be better. With this insight, she has developed new standards of cancer treatment in Canada and around the world. This has benefited millions of patients!

6

As a leader, she has brought together all sorts of different scientists together (basic and clinical), and also connected these researchers to policymakers. This team building helps make better science and better laws that can make these treatments more efficient and safer for cancer patients.

Art by Armin Mortazavi and text by Zahra Sepehri. October 2021

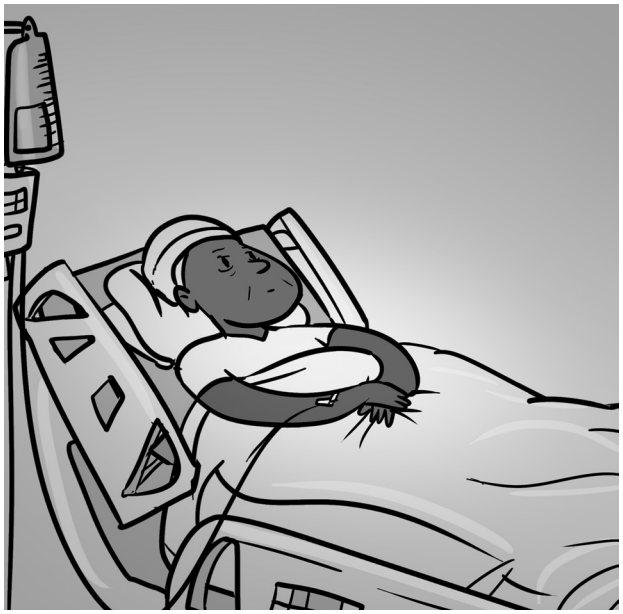
From the Lab Bench to the Hospital Bed.

The ins and outs of taking an anti-cancer treatment from discovery in the lab to the medicine you give to the patient.

Written by Zahra Sepehri and David Ng
Art by Armin Mortazavi

October 2021

Millions of people from across the world, young and old, suffer from cancer. In fact, during the time it takes for you to read this article (say about 10 minutes), 4 more Canadians will have been diagnosed with this disease. And part of the reason for its ubiquity is because cancer is actually a disorder representing several hundred different diseases.



At its essence, cancer happens because a cell has lost its ability to know when and where it needs to stop dividing. This can lead to abnormal cells that can live much longer, even to the point where they may become immortal, and also where they can grow and divide faster. As a result, this uncontrolled cell division can form masses or growths which are often called tumors.

Here, there are two major types of tumors: **solid** and **liquid**. Liquid tumors occur in your bodily fluids, such as blood, bone marrow, or lymph nodes. Both the bone marrow and your lymph nodes are active sites for immune cells to grow and develop. Consequently, liquid tumours that arise from these tissues constitute many of the cancers that we call **leukemias**. Solid tumors tend to be more compacted together, and usually grow within tissue. Examples include tumours in the brain, skin, breast, and many other organs.

Cancer and drugs

One common strategy for drugs that treat cancer is to take advantage of the disease's core characteristic. Because cancer cells grow and divide rapidly, this also means that they tend to be very active in securing nutrients and other things needed to maintain this level of growth. Consequently, many cancer drugs are ultimately toxic in nature, and administration is a balancing act in figuring out delivery and dosage so that the difference between what a cancer cell and a normal cell takes up is the difference between being killed or staying alive. This is also why when treating tumours, it's not uncommon for the patient to experience serious

side effects: it's a bit like they are being poisoned but in a very controlled fashion.

To minimize side effects, research into how the drug is delivered is just as crucial as the mechanism of the drug itself. Essentially, we want the drug to target the abnormal cells in a way that maximizes its positive effects, whilst minimizing harmful negative effects on the less active normal cells. Because of this, it is important to prescribe the treatment at the **correct dose**, at the **right time**, using the proper **route of prescription**, and for a **suitable duration**. All of these considerations can allow us to better and more precisely deliver the drug against the tumour so that the drug's **efficacy** (how well it works) is optimized, while minimizing the **toxic side effects** (essentially monitoring its **safety**). This is an area that many cancer scientists are working on, sometimes by doing tests on the cancer cells in petri plates but also sometimes by testing the drug on the cancer patients themselves.

Scientists and clinical trials for newly discovered targeted drugs

In medical science, research is sometimes categorized as the work of two major groups of scientists. Some scientists do their work within a strictly laboratory setting, working with cancer cells in very controlled scenarios. For instance, this might be where experimental variables of individual cells can be closely studied by monitoring effects in petri plates. These scientists put their primary focus on the molecular workings of actively growing cancer cells, and are often referred to as **basic research scientists**. In many ways, their work may focus on the treatment, but more often than not, they also represent the active investigation of basic cell functions. Other scientists, however, focus their attention on directly improving the quality of life for patients. They want patients to have longer and better lives, and perform experiments with patients to work out best practices in attaining that goal. These scientists are often referred to as **clinical scientists**.

The two are both equally important because they play roles in the pathway for any new treatment, as it moves from discovery to being used by patients. Basic scientists, working in their lab environment, produce results that lay the foundation for clinical scientists to do their experiments where safety and efficacy can be explored in the patient setting. Indeed, before being approved for final use, any novel therapy needs to pass through a variety of different phases of clinical trials.

Still, one of the challenges is coming up with guidelines to determine which therapies should progress from basic science discovery to clinical

science testing. At any given moment, there are very large numbers of basic scientists working in their labs, producing data and proposing new and different ways to treat a tumor. Out of all of the proposed ways, who decides which discovery is worth being a candidate to be tested in clinical trials?

Furthermore, these guidelines should not only provide direction on which novel therapies should be allowed to start clinical trials, but they should also dictate how trials need to be worked through, as well as when and why a clinical trial needs to terminate. In other words, it's important to set boundaries for this clinical research, so that the patient's quality of life is always considered above all else.

Team building and optimization of treatments

This is where Dr. Elizabeth Eisenhauer came in. Dr. Eisenhauer is a Professor Emerita in the Department of Oncology at Queen's University and this year's Canada Wightman Gairdner Award winner. For over 30 years, she has made groundbreaking contributions on how anti-cancer drugs are clinically evaluated.

Reminiscing about her early career, she notes, "There was a certain amount of good luck in finding an excellent mentor," referring to her colleague Dr. Joseph Pater who in 1982 offered her a position in helping found the *Investigational New Drug Program* (IND) of the then *National Cancer Institute of Canada Clinical Trials Group*. From there, she oversaw the direction of the IND program and has had many other leadership roles in the field. In all those years, she has tackled cancer from different aspects: treatment, supportive care, and prevention.

As a leader, she saw the importance of bringing basic scientists and clinical researchers together, so that this collaborative approach could lead to better science. Actively connecting the two also allows for better administration of the research: for example, it can help funding organizations navigate new partnerships that allow investments to be more strategic, filling in gaps in the landscape of cancer research.

Dr. Eisenhauer also recognized the crucial task of connecting researchers to policymakers. This was especially important in her work around cancer prevention and tobacco, as the science itself is only as powerful as having government systems in place that can help society adopt healthier habits. Here, her work has led to the *Tobacco Endgame for Canada*, a collection of policy measures aimed at cutting the prevalence of tobacco use to less than 5% of the Canadian population by the end of 2035.

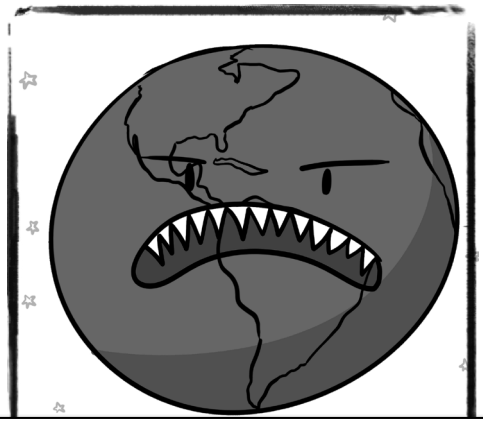
Early on, Dr. Eisenhauer also recognized that not everything needs to be new to be better. Essentially, there may be opportunities to optimize the efficacy of existing drugs, by simply reevaluating treatment approaches. Furthermore, she saw the value in emphasizing patient input in this process.

In this manner, she showed that **Taxol**, already one of the most widely used cancer drugs in the world, could be administered in shorter and safer ways to maintain efficacy but with significantly fewer side effects. These methods are now internationally recognized as standard practice for Taxol to the benefit of millions. In fact, her expertise in clinical evaluation has coordinated more than 170 different clinical trials on a diverse array of anti-cancer medications all across the world. This in turn has been pivotal in establishing many new and effective treatments for ovarian, skin and brain cancers.

Overall, it's clear why Dr. Elizabeth Einsenhauser has been awarded the prestigious 2021 Canada Wightman Gairdner Award. Her scientific leadership and ability to bring different communities together has been responsible for fundamental, impactful and extraordinary contributions in how anti-cancer agents and clinical trial methodologies are evaluated. As she says, to fight a disease as complex as cancer, "It is not just one part of science that has to progress, but all parts of it need to move progressively forward."

Virus Trackers and Preventing Pandemics

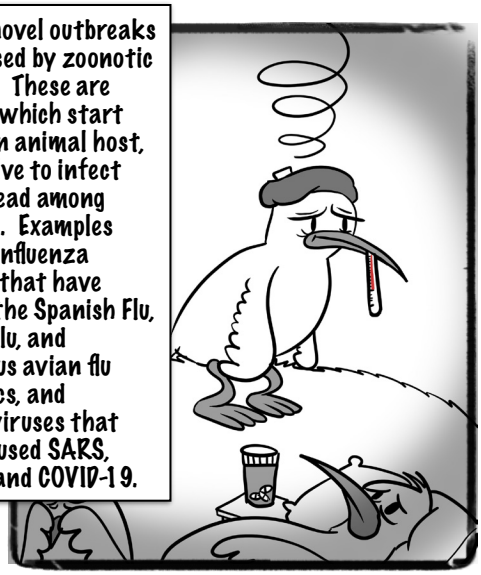
1



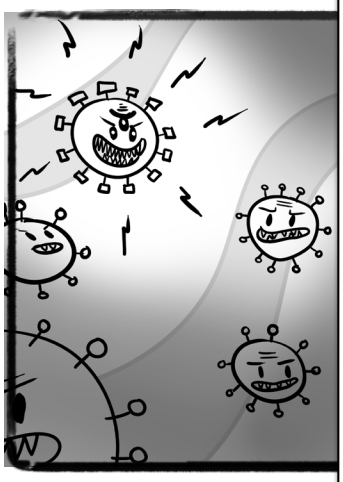
A pandemic is when a disease is so infectious that it can spread across a country or even globally. The world has faced numerous viral pandemics throughout history.

2

Many novel outbreaks are caused by zoonotic viruses. These are viruses which start off in an animal host, but evolve to infect and spread among humans. Examples include influenza viruses that have caused the Spanish Flu, Swine Flu, and numerous avian flu epidemics, and coronaviruses that have caused SARS, MERS, and COVID-19.



3



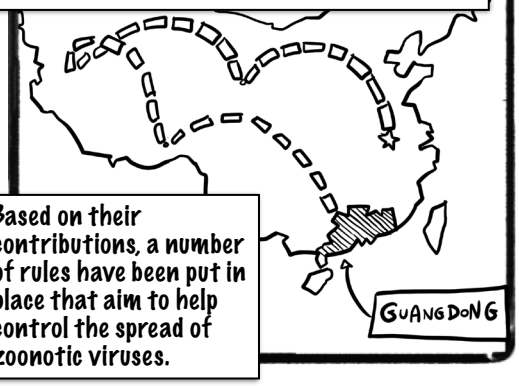
Many viruses can mutate quickly. They can make mistakes when they replicate, or even swap genetic material with other strains if they infect the same cell. These changes can give zoonotic viruses new ways to infect humans and can also make it challenging for our immune systems to combat them.

4

Dr. Peiris and Dr. Guan have been researching viruses for over 20 years. They have tracked influenza strains in birds, pigs, humans, and other animals, to understand the evolution of zoonotic viruses and monitor their risk of causing pandemics in humans.

5

In 2003, Dr. Peiris did important work to discover that the first SARS outbreak was caused by a coronavirus. And Dr. Guan played a crucial role in tracking the zoonotic disease to wild animal markets in Guangdong.



Based on their contributions, a number of rules have been put in place that aim to help control the spread of zoonotic viruses.

6

Overall, Dr. Guan and Dr. Peiris have helped respond to novel influenza and coronavirus outbreaks throughout their scientific careers, and their work continues to be crucial in helping the world prepare for future pandemics.

Art by Armin Mortazavi and text by Nicole Wang. October 2021

Virus Trackers and Preventing Pandemics

The best pandemic response is to be prepared, before animal viruses infect humans

Written by Nicole Wang
Art by Armin Mortazavi

October 2021

In the year 2021, the topic of pandemics, a scientific term that describes a disease outbreak of global proportions, has been inescapable. This is because the world has been (and still is) dealing with the all-encompassing effects of the COVID-19 pandemic.

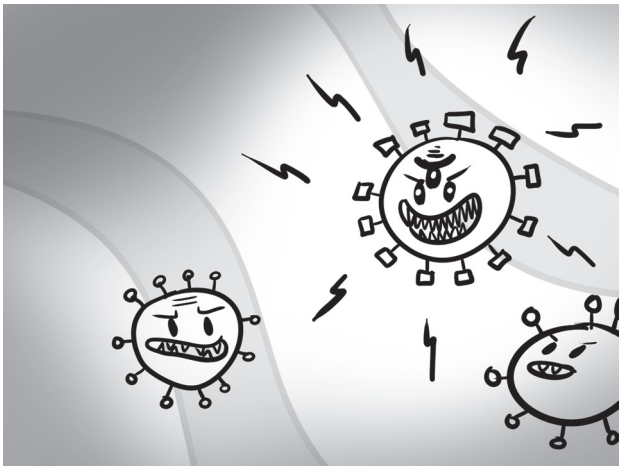
But pandemics aren't a new phenomenon and it's easy to forget that the world has seen and survived viral pandemics throughout history. Just within the last 20 years, there have been pandemic outbreaks of viruses that caused Severe Acute Respiratory Syndrome (SARS) in 2002, the H1N1 Swine Flu in 2009, and the Middle East Respiratory Syndrome (MERS) in 2015.

However, you're also probably aware that being infected by viruses is something that happens all the time. People regularly get sick from common colds or the seasonal flu. These viruses can make you ill, but don't seem to cause devastating outbreaks. So what makes a virus like SARS-CoV-2, the one responsible for the COVID-19 pandemic, especially dangerous?

Comfort in the familiar

The primary difference between viruses that cause common diseases, and those that cause pandemics boils down to familiarity. In effect, there is a benefit to having already seen certain infections, because common colds are "common," and seasonal flus are "seasonal."

Our bodies are trained to fight viruses in a variety of ways, and this includes specialized immune memory cells that can remember a virus that they've encountered before. These cells essentially act as an early warning system should a person be re-infected with the same virus, or even another virus that has strong similarities. This in turn leads to a much quicker and stronger immune response that often results in milder, or even no infection.



Add to this, we also have the luxury of effective ways to predict and therefore prepare for outbreaks of these common viruses. For instance, as part of global health initiatives, scientists around the world diligently track the seasonal flu: where it is spreading and also whether there are genetic

changes that could be cause for concern. Using this information, they can predict what the next version of the flu might look like, and ready the production of useful flu vaccines. These flu shots are designed to proactively trigger those memory cells that can provide protection before the seasonal flu actually comes to town.

Ultimately, we are less concerned with these common viruses because our immune systems have seen them before, either by way of past infections, or through proactive vaccine initiatives. This familiarity means that rapid rates of infections tend not to occur making them less of a threat to global health.

The hidden threat of zoonotic viruses

Meanwhile, unfamiliar or novel viruses are a completely different beast. If a virus is new to human society, they can enter our bodies, cause sickness, and spread quickly, all before our immune systems even have a chance to properly react. This is usually how a pandemic might start: essentially, the world is immunologically naive to the disease. It's also important to note that some of these pandemic viruses may be no deadlier than the common viruses, but without the protection of immunological memory, we end up facing the full force of the virus and higher rates of infection. The virus can therefore spread rapidly within a population and beyond, sometimes to devastating effects.

Many of these viruses are zoonotic, meaning that they were originally only able to infect certain animals, but over time have evolved the ability to infect or "jump" to humans. This can happen because when viruses make copies of themselves, the replication of their genetic code can result in mistakes, small copying errors or even drastic swapping of genetic material, leading to random changes called mutations. Although these changes are usually inconsequential or even harmful to the virus, some mutations might give a virus an edge to cause disease.

Luckily, only a very miniscule proportion of animal viruses will evolve to infect humans, as they need to overcome many barriers to infect a new species. For example, the virus will likely need mutations that: (1) allow recognition of human cells; (2) provide some protection against the human immune system; and (3) infect in ways that allow efficient spread from person to person.

This is why the "jump" is more likely to happen in situations where people are frequently exposed to infected animals. This can happen, for example, at live animal markets, during livestock transportation, or even in situations where habitat loss cause wildlife to be forced into new areas. Such environments could be the unwitting origin points for a pandemic.

Although jumping from an animal to a human host is rare, these zoonotic viruses are potentially very dangerous to global health. They are globally unfamiliar. Because of this threat, one of the best ways to stay prepared for a zoonotic virus is to attempt to track it before it spreads to humans.

Staying prepared and predicting pandemics

While research can't predict exactly when a pandemic will occur, studies have shown that you can predict which animal viruses are the most likely to cause novel disease outbreaks. Here, scientists

Dr. Joseph Malik Peiris and Dr. Yi Guan, winners of the 2021 John Dirks Canada Gairdner Global Health Award, have done pivotal work on this type of surveillance. They have been collaborating since the 1997 H5N1 avian flu outbreak in Hong Kong (caused by an influenza virus), and continue to be extremely involved in international efforts to track viruses in animals.

In this case, potential hosts such as wild birds, chickens, pigs, and humans are routinely sampled for influenza viruses. This sampling allows scientists to track mutations in the genetic sequences of these viruses. They monitor whether these viruses have jumped between different animal hosts in the past, as well as evaluate whether they can cause disease. All of these considerations help to predict whether these viruses might pose a threat to human health. Over time, this data has also allowed scientists to understand the evolution of zoonotic viruses in their natural hosts, and figure out key mutations important for their jump from animals to humans.

Based on their studies, Dr. Guan and Dr. Peiris have provided warnings about avian flu subtypes that have the potential to cause pandemics in humans. And in order to protect against these threats, they have published many protocols on pandemic preparedness and have suggested ways to prevent the spread of zoonotic influenza viruses, including measures to close live animal markets, as well as develop strategies to quickly produce vaccines for high-risk influenza strains.

Virologists in action: How to deal with novel outbreaks

When a novel outbreak occurs, there are a number of key objectives to work towards. First, it's important to figure out the source (for instance the animal of origin in zoonotic cases) to prevent it from further infecting new people. Second, there needs to be an effective way to diagnose and track the disease in humans so that spread can be monitored. And of course, in order to treat the disease, work needs to be done to understand how the virus interacts with and affects human cells.

In late 2002, a novel viral outbreak appeared in Guangdong, China, and started to spread worldwide. Due to their experience tracking zoonotic influenza viruses, Dr. Guan and Dr. Peiris immediately got to work, initially thinking that this mysterious disease might be caused by an influenza strain. However, their research groups soon realized this was not the case and became the first to identify that the new infectious disease, known as SARS, was actually caused by a coronavirus called SARS-CoV.

Dr. Guan's team was the first to isolate the coronavirus from wild animal markets in Guangdong, China, showing that it was a zoonotic virus as well as the importance of closing animal markets. Meanwhile, Dr. Peiris's team developed tests that could quickly and non-invasively detect the virus in patient samples, and began work to uncover how SARS-CoV was causing disease. The work of these two scientists was critical for the early diagnosis of SARS, helping doctors effectively treat patients, and helping public health agencies and the scientific community to track the spread and evolution of the disease worldwide. Their work greatly contributed to the eradication of the SARS pandemic, to the point where the outbreak was ultimately controlled by testing and isolating those who were sick, before a vaccine was even needed.

In addition to working with SARS, Dr. Peiris and Dr. Guan have also contributed to research on subsequent coronavirus pandemics, MERS and Covid-19. They also remain very active in tracking influenza viruses in animals, especially those with a high pandemic risk.

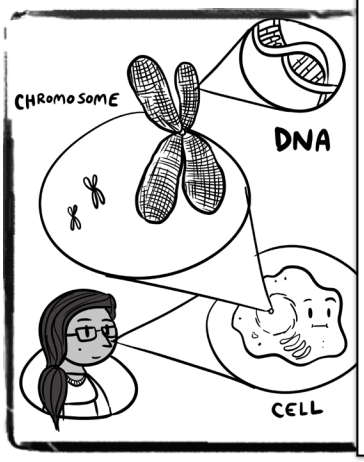
Importance of global collaboration

Dr. Peiris looks back fondly at the memories and collaborative relationships he developed throughout his career. He also credits the rapid de-escalation and control of the SARS pandemic to the global effort organized by the World Health Organization, who hosted daily meetings between scientists around the world to discuss new hypotheses, data, and challenges. “I don’t think we would have been able to resolve this fairly quickly, if not for this daily sharing of information,” Dr. Peiris recalls.

Overall, the research of Dr. Peiris and Dr. Guan powerfully exemplifies the importance of scientific collaboration. Global cooperation is essential to solve global challenges, whether it is preventative (such as tracking animal viruses around the world), or reactive (fighting a pandemic). As we currently deal with the enormous impacts of the COVID-19 pandemic, and as we look towards the possibility of future pandemics, we can be grateful for the groundbreaking work of Dr. Peiris and Dr. Guan.

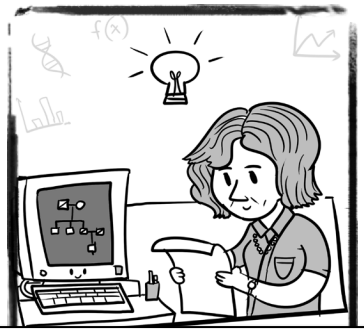
Discovering the Breast Cancer Gene

1



Our DNA codes for a blueprint that makes you, you! This information is organized into working units called "genes, which in turn are found on 23 pairs of chromosomes. All of this DNA is packed into each and every cell in your body. Today, we know that deciphering the code in your genes can give us clues on your risk of developing certain types of cancers, such as breast cancer.

2

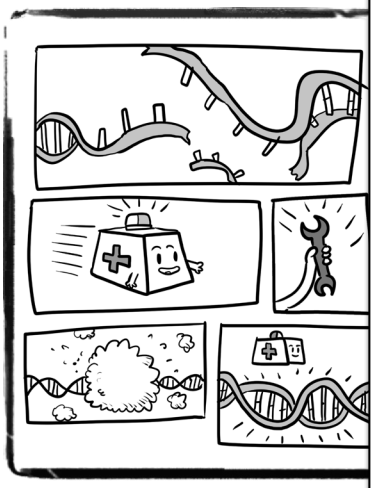


Scientist Dr. Mary-Claire King was one of the first to investigate this, and she did this by first using math to monitor families with breast cancer. Here, she found that tracking these breast cancer cases led to calculations that strongly suggested genetic inheritance of the disease.

3

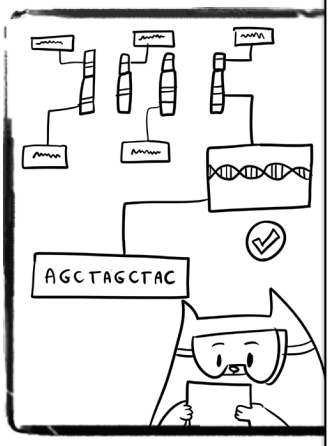
However, she still had to find a gene responsible. In 1990, she was able to use new technology to pinpoint the gene to a region on chromosome 17. From there, the race was on to sequence and characterize this gene.

4



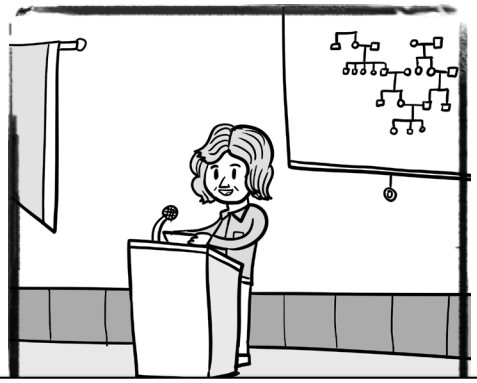
This gene became known as the Breast Cancer 1 (BRCA1) gene. BRCA1, and its sister gene, BRCA2, both encode proteins that function as tumour suppressors. This means that they actively try to stop cancer from starting. BRCA proteins are important in repairing DNA breaks, which helps protect cells from cancer causing mutations.

5



Now, people can have their genes sequenced to determine if they have any mutations in their BRCA1 or BRCA2 genes. Finding a mutation could mean that the BRCA is not working properly and therefore makes the person more susceptible to harmful DNA mutations. This allows patients to take preventative action to help lower their risk of developing cancer.

6



Dr. Mary-Claire King's lasting legacy in the cancer field is the revolutionary idea that cancer could be genetically inherited. This is a crucial part of cancer research as scientists now recognize that there are many genes involved in the development of human cancers.

Art by Armin Mortazavi and text by Sarah LaFramboise. October 2021

Discovering the Breast Cancer Gene

Using math to find the link between cancer and genetic inheritance.

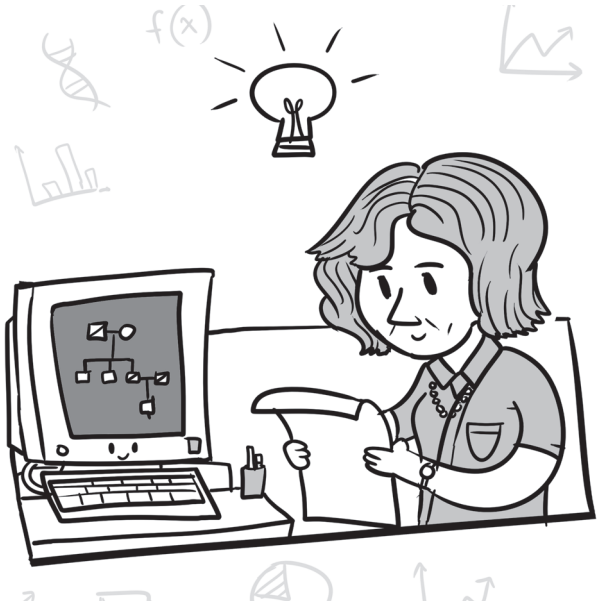
Written by Sarah Laframboise
Art by Armin Mortazavi

October 2021

You probably know at least one person who has been affected by cancer. In fact, statistics show that almost half of all Canadians will develop cancer at some point in their life. Cancer occurs when cells malfunction and multiply uncontrollably. This is similar to weeds in your garden that can overpopulate and take over. This loss of control develops into large growth of cells, known as tumours, which can impede the functioning of surrounding tissues.

There are over 200 different types of cancer from all different parts of our body, and most are named after the location where they occur. One example of this is breast cancer. Here, you may have participated in some of the popular fundraising activities, like walks or races, where money is raised for breast cancer research. In addition, you may have seen the pink ribbons that are used to represent the cause. Breast cancer is currently one of the most common types of cancer, affecting 1 in 8 women in Canada.

Scientists still haven't completely worked out all the causes of breast cancer, but originally, it was thought that the development of this disease was primarily due to environmental factors such as toxins or viral infections. This all changed in 1970, when Dr. Mary-Claire King, one of the 2021 Gairdner International Award winners, hypothesized that there may be **genetic markers** in our DNA that could influence one's likelihood to develop breast cancer. In the same way that DNA can encode for things like hair colour, she wondered if DNA could also encode for susceptibility to the disease.



What is a gene and how do we inherit them from our parents?

Dr. King noticed that many women who had breast cancer, also had mothers who had breast cancer. This suggested to her that breast cancer could be the result of DNA mutations that are inherited.

In order to understand how breast cancer can be passed through generations, it is important to understand the concept of genes. A **gene** is usually

thought of as a discrete sequence of DNA code that results in or influences a characteristic. Because there can be variations in the sequences of the gene, the characteristic may exhibit itself in different ways. For example, hair colour can come in many forms, and it is the variation in the sequence of genes involved in hair colour that causes the actual different colours.

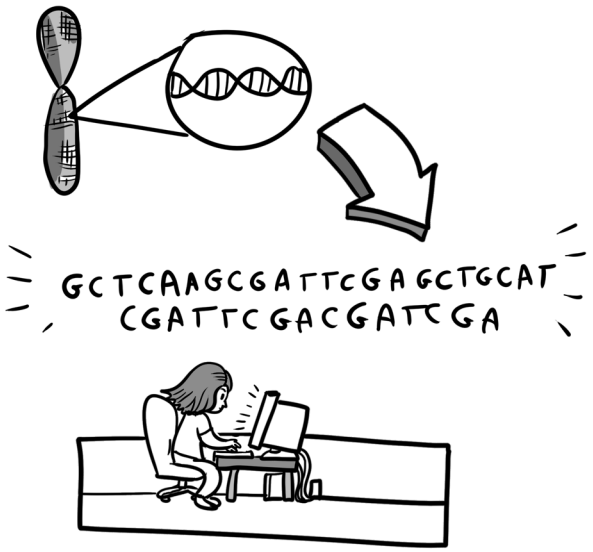
In terms of terminology, differing variations in a gene are referred to as differing **alleles**. Importantly, for any given gene, our DNA blueprint is such that we inherit one allele from our mother, and one allele from our father, creating an allelic pair that ultimately results in how the characteristic turns out. Geneticists call this output your **phenotype**. For example, if you have brown coloured hair - brown would be your hair colour phenotype.

Because your phenotype can be influenced by the alleles you inherit from your parents, characteristics tend to be hereditary in nature. Put another way, phenotypes can be passed down from generation to generation. Note that there are many inheritance patterns that your genes can follow that affect your phenotype. In particular, one common way is to think of alleles as being **dominant** or **recessive**. In this case, if a dominant allele is inherited from one parent, its resulting phenotype dictates the final outcome, effectively overpowering the recessive allele of the other parent. This can be dangerous if the dominant allele carries a mutation that results in a harmful phenotype.

The Discovery of the "Breast Cancer Gene"

Coming from a background in mathematics and evolution, Dr. King was able to examine the incidence of breast cancer, using large sets of data from over 1500 families. And since the world of genetics was still in its infancy in 1970, Dr. King relied heavily on using mathematical methods to calculate if there might be inheritance patterns that were suggestive of the disease being caused by a single gene.

Her results conclusively showed that in about 4% of families, there appeared to be a clear dominant method of inheritance. Although this seems like a low percentage of the total dataset, for those in the 4%, there was a substantial impact in that the math predicted up to an 82% likelihood of developing breast cancer before the age of 70.



However, due to limitations of technology at the time, she was not able to identify the specific gene and allele responsible for this observation. Indeed, it wasn't until 1990 that Dr. King and her team were able to employ new technologies allowing

In addition to her revolutionary work on the BRCA genes, Dr. King has numerous other achievements in the field of genetics. Her PhD work investigated similarities between humans and chimpanzees, with the shocking discovery that our genetic codes are 99% similar.

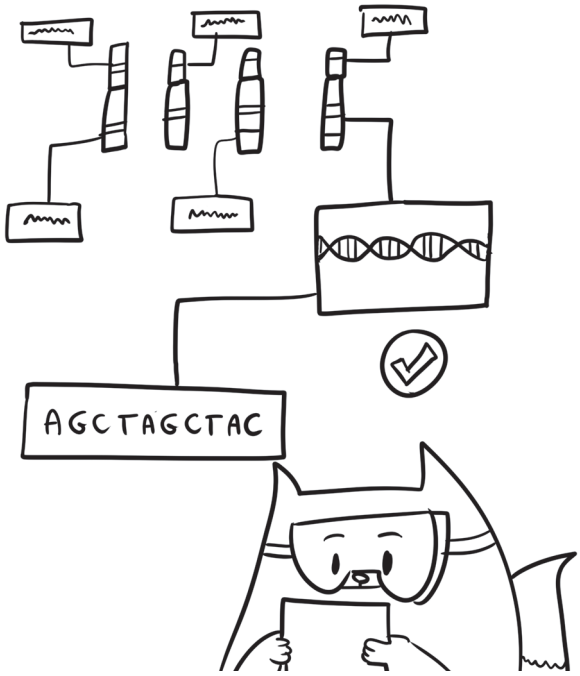
As well, during the 1980's, she began a collaboration with the human rights group Abuelas de Plaza de Mayo (Grandmothers of Plaza de Mayo), that reunited grandparents with children kidnapped during the war in Argentina. Here, she developed a specialized DNA sequencing test that could be used to prove the relationship between grandparents and children who were left without parents or born into captivity. Even later, this test was used to identify the remains of soldiers in Vietnam, Korean, and WWII.

"Those of us who work in science have a responsibility to present facts and speak truth about issues that we know well," Dr. King declared. She has continued to do just this by advocating for human rights issues, and has been a continued voice for equality and women's rights.

them to identify a small region of the genome that was associated with increased inheritance and likelihood of developing early-onset breast cancer.

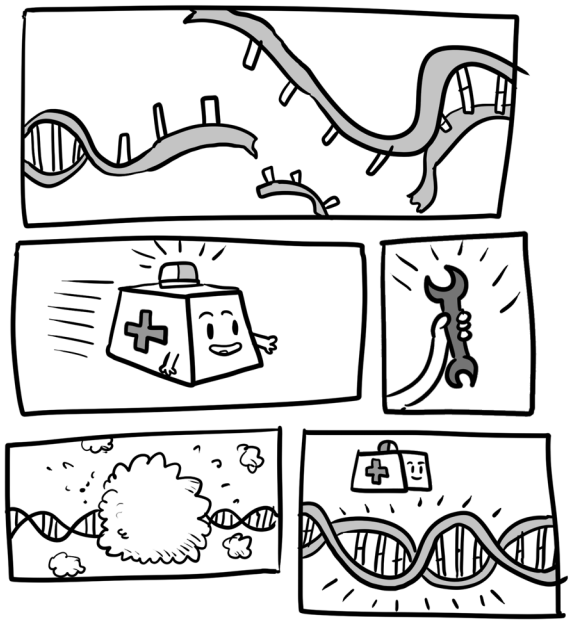
She reflects: "Once this hypothetical breast cancer susceptibility gene was mapped to a patch of chromosome 17, it was clear to many people in the public and private sectors that the gene was real" As a result, the race was on to find and characterize the **Br**east **Ca**ncer **1** gene, or **BRCA1** gene as it is known today.

It wasn't until 1994, that the BRCA1 gene was finally cloned and sequenced. In this case, the winner of the race was a group at the biotechnology company, Myriad Genetics. By examining the gene in breast cancer patients, the company was able to identify several mutations in the BRCA1 gene that could result in increased breast cancer risk. Later that year, Myriad Genetics also sequenced and characterized another breast cancer gene, **BRCA2**, and the company was subsequently awarded a patent on the two genes. This allowed them to provide commercial genetic testing for hereditary breast and ovarian cancer.



What is BRCA1 and BRCA2's function in cancer?

With advances in technology and our understanding of genetics, we now know much more about



the function of the BRCA1 and BRCA2 genes. In particular, we can understand how mutations in these genes can lead to phenotypes of increased risk of breast and ovarian cancer. Here, the BRCA1 and BRCA2 genes encode proteins known as tumour suppressors. These can act to directly protect cells from DNA mutations, and in doing so, suppress the formation of cancerous cells. More specifically, when damage or breakage of DNA is caused by radiation or other environmental factors, these proteins function to repair those errors. You can imagine that if a person has alleles of BRCA1 or BRCA2 that work less efficiently, they will be more prone to accumulating harmful mutations which leads to the increased likelihood of disease.

Impact on the Cancer Field

Dr. Mary-Claire King's lasting legacy in the cancer field is the revolutionary idea that cancer could be genetically inherited. Her expertise and diverse background had allowed her to view things from a different angle. With a bit of mathematics and molecular biology, her findings shifted the cancer field to investigate genetic inheritance of mutations underlying different types of cancer.

Nearly 40 years later, Dr. King continues to lead ground breaking research on the BRCA1 and

BRCA2 genes, now using the most advanced sequencing technologies and genetic tools.

Thanks to Dr. King's discovery, people with a family history of breast and ovarian cancer are able to get genetic testing to examine their BRCA1 or BRCA2 genes. This information informs them of their risks of getting the disease in their lifetime. Knowing that they have these mutations is powerful because it allows for patients to seek preventative measures against these forms of cancer.

ACTIVITIES AND DISCUSSION QUESTIONS FOR CLASSROOM USE

Most suitable for Grades 11 and 12, but some content can also work for Grades 8 to 10.

Daniel Drucker, Joel Habener, and Jens Holst:

Read: F. Qaiser and A. Mortazavi. "**The Molecular Elements of Diabetes**" (article, comic and/or video). *Canada Gairdner Awards 2021 Laureates Education Materials,* pp2 - 6

Learning Objectives:

1. Define blood sugar homeostasis.

2. Clarify the roles of insulin and glucagon in managing blood glucose levels.

3. Define an incretin.

4. Describe the role of proglucagon as a gene and GLP-1 and GLP-2 as peptides.

5. Characterize the role of an inhibitor as treatment for disease

6. Understand GLP-1 and GLP-2 as treatments for type 2 diabetics and short bowel syndrome.

Supplementary Reading:

Keywords: insulin, glucagon, proglucagon, glucagon-like peptide-1, glucagon-like peptide 2, dipeptidyl peptidase-4

Our bodies want to be in a healthy state and we call this **homeostasis**. For us, healthy means to be in a stable equilibrium (or balance) between interdependent elements, specifically maintained by physiological processes. Humans' internal body temperature is a great example of homeostasis. When someone is healthy, their body maintains a temperature close to 98.6 degrees Fahrenheit (37 degrees Celsius). When you get shivery in the cold, or sweat in the summer, that's your body trying to maintain homeostasis.

Our bodies are constantly at work maintaining **glucose homeostasis** - the balance of insulin and glucagon to maintain blood glucose. Glucose is a sugar that we consume and our bodies have to decide to either use it immediately to make energy or to store it for energy later. Our bodies know which choice to make through hormone signalling, like what insulin and glucagon do. Insulin is secreted by the pancreas in response to elevated blood glucose after a meal. Insulin lowers blood glucose by increasing glucose uptake in muscle and adipose tissue. A fall in blood glucose increases the release of **glucagon** from the pancreas to promote glucose production to raise blood sugar levels.

Proglucagon is a protein encoded from a gene and the precursor of glucagon. It is also generated in the pancreas and cleaves into several components in different organs. **Glucagon-like peptide 1** (GLP-1) and **glucagon-like peptide 2** (GLP-2) are cleaved from proglucagon and secreted at the intestine.

GLP-1 is an **incretin**; thus, it has the ability to decrease blood sugar levels in a glucose-dependent manner by enhancing the stimulating the release of insulin. People who suffer from **type 2**

diabetes are insulin resistant meaning that their cells don't respond well to insulin and have a tough time taking up glucose from the blood. As a result, the pancreas attempts to create more insulin. GLP-1 as a treatment for type 2 diabetes is attractive because it enhances insulin secretion. Normally GLP-1 would be degraded by **dipeptidyl peptidase-4** (DPP-4). In the treatment plan of a type 2 diabetic DPP-4 inhibitors may be included to disrupt this pathway. A way to avoid DPP-4 would also be to find a GLP-1 analogue that is comparable to GLP-1's activity.

GLP-2 is also cleaved from the proglucagon at the intestine. This peptide enhances intestinal growth and metabolism with nutrient intake. Ultimately GLP-2 enhances intestinal function. GLP-2 and related analogs similar to it may be treatments for conditions like **short bowel syndrome**. In this condition the body is unable to absorb enough nutrients from the foods you eat because you don't have enough small intestine. The small intestine is where the majority of the nutrients you eat are absorbed into your body during digestion..

Classroom Activity: Symptom Scenario

Supplies: one piece of paper per group and a pen.

Time: 15 minutes for activity, 15 minutes for discussion.

Description: Break the students up into groups of three. In this activity, each student will represent one of the three symptom scenarios listed below:

Student 1: fatigue between meal times, alert, normal washroom times and types

Student 2: increased thirst, frequent urination, fatigue, increased hunger

Student 3: stomach ache, diarrhea, weight loss, fatigue

Once the students have their symptom prompts they will begin discussing with their group what could possibly be wrong (hint: there were two abnormal conditions mentioned in the article and supplemental reading). Have them write down their symptoms and the name of their current state as well as any treatment options that may be available to them.

Purpose: The purpose of this activity is to work through the information discovered by Holst, Drucker, Habener and apply it to a real-life scenario. By organizing the conditions that correctly match the symptoms and recommending treatment, students will better understand endocrine signal transduction and glucose homeostasis.

Discussion Questions:

1. Insulin and glucagon are antagonistic hormones in the body because they oppose or reverse the effect of one another. Can you think of other examples of hormones that are antagonists?

2. When administering things like GLP-1, GLP-2, or DPP-4, do you think dosage is important? Why?

3. If you were to make a flowchart of the various hormones and peptides involved in glucose homeostasis, you may realize that controlling this appears very complicated with many parts involved. Why do you think this complexity is a good thing? Another way to think about this is to imagine what if homeostasis was controlled only by a single thing - why might that be a bad thing?

Activity designed by Rhonda Thygesen.

Elizabeth Eisenhauer:

Read: Z. Sepehri, D. Ng, and A. Mortazavi. "**From the Lab Bench to the Hospital Bed**" (article, comic and/or video). *Canada Gairdner Awards 2021 Laureates Education Materials,* pp7 - 11

Learning Objectives:

1. Understand three treatments for cancer (chemotherapy, HAP, angio).

2. Define treatment toxicity.

3. Understand the importance of scheduled planning for drug treatment.

4. Able to describe acquired resistance. Identify acidic invasion.

Supplementary Reading:

Treatment of cancer requires effort from basic research scientists and clinical researchers, as mentioned in the article. Treatments developed in the lab will be tested by clinical researchers on existing cancer patients to figure out the best method of therapy. As you can imagine, there are multiple factors that play into the success of a treatment that clinical researchers must observe, some of which were previously discussed.

Chemotherapy is a very popular type of cancer treatment that uses one or more anti-cancer drugs as part of a standardized routine. However, while the purpose of chemotherapy medications is to reduce your cancer symptoms and lengthen your life, the drugs can also have unwanted effects on your body. Chemotherapy can poison your body and lead to harm, and this is known as treatment toxicity, a main indicator of how a patient is responding to the chemotherapy course.

Just as important as the type of treatment is the scheduled planning of it. By determining when a treatment will be administered researchers can predict and avoid a poor bodily response in the patient. Sometimes the body will react in unexpected ways such as with acquired resistance. Tumors that suddenly begin to grow while on a treatment regimen may be experiencing tumor resistance. In this case, researchers have to balance between slowing the tumor growth and causing resistance. Certain cancer cells may have hyperactive metabolisms that break down carbohydrate fuel at abnormal speeds, resulting in what's called acidic invasion. The acid produced from a tumor kills normal cells and allows it to grow faster.

Hypoxia activated prodrug (HAP) is a nice complement to chemotherapy, but it only works in hypoxic regions - areas with low oxygen. In a patient, a mix of chemotherapy and HAP may be necessary. This is called combination therapy. Angio drugs block angiogenesis - the growth of blood vessels. They do this by blocking nutrients and oxygen from a tumor, essentially starving it. Angio can boost the effectiveness of HAP by lowering the amount of oxygen in the tumor, inducing hypoxia (low levels of oxygen in your blood).

All three drugs (chemotherapy, HAP, angio) can be used to treat a cancer patient. One patient's cancer treatment may look very different from another's and requires unique treatment plans.

Classroom Activity: Cancer Crusade!

Supplies: Students will need to download a free app. Therefore access to a smartphone or computer (laptop or desktop) and to the Apple app store or the Google Play store is required

Time: 5 minute scenario/student, adjust total time as necessary for activity (for instance, students can go through 2 scenarios in 10 minutes, etc). 15 minutes for discussion.

Description: Students will download the game "Cancer Crusade" onto a smartphone or a computer. If possible, have them pair up in groups of two to share a device and work through the app together. The students will run through the instructions of how the game works and then will begin digitally experimenting to treat tumour growth. By playing the game, the students will be testing different variations of treatments, becoming real-life data for cancer researchers. Students will receive a good score in the game by preventing both tumor size and toxicity from becoming too high for too long.

Purpose: Many combinations exist for cancer treatments, however, it is difficult to know how much, at what time, and for how long. Students will play the role of a clinical researcher from their cell phones and laptops and observe how a fake cancer cell grows and shrinks in response to their treatments. By playing the game and testing out new possible treatment combinations the students are contributing to research collections that otherwise would have taken years of trial and error.

Discussion Questions:

1. How did it feel to be responsible for finding the right treatment and dose? Was it frustrating or exciting? Did anyone have a particularly good score?

2. What do you think is the biggest challenge a clinical researcher faces in their day to day work?

3. What are some ways we can improve cancer research, specifically between basic research scientists and clinical researchers?

4. Tumors occur in many parts of the body resulting in breast, lung, brain, skin, and other associated organ cancers. How might you think treatments of these individual cancers would vary in dosage, method of administration, time of treatment, and length of treatment?

5. Politicians tend to fund clinical research rather than basic research, why do you think this is?

6. A pharmaceutical company seeking FDA approval to sell a new prescription drug must complete a five-step process: discovery/concept, preclinical research, clinical research, FDA review and FDA post-market safety monitoring. What do you think is the most difficult part and why? What specific challenges might each of these steps face?

Activity designed by Rhonda Thygesen.

Yi Guan and Joseph Malik Peiris:

Read: N. Wang and A. Mortazavi. "**Virus Trackers and Preventing Pandemics**" (article, comic and/or video). *Canada Gairdner Awards 2021 Laureates Education Materials,* pp12 - 16

Learning Objectives:

1. Describe what a virus is.

2. Explain the role of memory cells in viral infections.

3.Discuss some reasons for tracking viruses.

4.Describe what zoonotic viruses are and explain why they present a larger threat to humans.

5.List the three main objectives that scientists have when a virus outbreak occurs.

Supplementary Reading:

Memory cells are a critical component of our immune response, as they are how we remember viruses we have encountered before. Memory cells are made after our first encounter with a virus, so that the next time we are infected by the same virus (or a similar virus), our immune system can recognize it and jump into action much more quickly.

In the last two years we have all experienced and witnessed the effect that viruses can have on society. When a virus outbreak or pandemic occurs, not only is it important to understand how the virus is spreading, but it is also critical to gain an understanding of how the virus works. Scientists work hard to identify the source of the virus, develop a diagnostic measure and treatment, as well as learning how the virus interacts with human cells. An understanding of the biological mechanisms behind the virus and disease are crucial to develop a vaccine, and in some cases, a cure.

Classroom Activity: Tracking a Virus.
A virus tracking simulation followed by a discussion period. Students will represent sharing close contact with each other by mixing the water in each others' cups. After several exchanges, a chemical indicator will reveal "virus" present in some of the cups, and students will try to uncover who the original "infected" students were.

Supplies:
- 24-32 clear plastic drink cups, ½ cup to 1 cup in size (1 per student, for best results should be a multiple of 4)
- Water, about 1 liter
- Phenolphthalein solution, about 5 ml
- Sodium carbonate (aka washing soda), 1 scant teaspoon
- Disposable pipette or eye-dropper
- Beaker, flask, or cup
- Permanent marker
- 24-32 index cards

Optional:
- 24-32 small test tubes (1 per student, for best results should be a multiple of 4)
- Test tube rack

Time: 15 minutes for simulation, 15 minutes for virus tracking, 5-10 minutes for discussion

Description:

Set up:

1. Set the cups out on a table and optionally place the test tubes in the rack. Using a permanent marker, number the cups 1 to 24, 28, or 32, depending on class size. Please read the information about class size in step 3 of the Conducting the Simulation section (below) before you start! Number the test tubes in the same way. It is important that the total number of cups and test tubes used is a multiple of four.

2.Put about a cup of water into the beaker, and stir in one scant teaspoon of sodium carbonate (washing soda) until it is all dissolved and the water is clear. Choosing three of the numbered cups at random, pour this solution into them so that each cup is about one-quarter full. If choosing to use the test tubes, then pour some of the remaining solution into three of the test tubes whose

numbers correspond with the cups, so that each test tube holds about an inch of solution.

3. Fill the other cups about one-quarter full with water. Fill the remaining test tubes with about one inch of water. Put the test tubes somewhere out of sight.

Conducting the simulation:

1. Give each student an index card on which to write their name. Have each student obtain a prepared cup, and then write the number that appears on the cup next to their name on the index card.

2. Explain to students that they will each "share close contact" with three other students, one at a time, following a certain procedure:

- After choosing a classmate to "be in close contact" with, one member of the pair pours all the water from their cup into the partner's cup. Then the partner will pour half of the combined liquids back into the first member's cup. This way the students have mixed their two liquids, but in the end, each has the same amount they started with. Both students should record the number of the cup belonging to the person they just exchanged liquids with. (Demonstrate this exchange process with two extra cups containing tap water, emphasizing the need to record the numbers of the cups.)

- Repeat this "close contact" 2 more times, for a total of 3 exchanges. Ensure the students record the number of the cup that they are in contact with each time.

3. Note: This number 3 is important for the problem solving aspect of the exercise that follows. It is also important that the total number of participants is a multiple of 4, so classes of 24, 28 or 32 will work perfectly. If you don't have quite enough students to make a multiple of four, it is best if you recruit extra students or adults (including yourself) rather than leave any students out. Any recruits need only be present for the few minutes it takes to do the liquid exchanges. If you have 20 or fewer students, use only two "infected" cups (and test tubes) for the simulation, instead of three.

4.Have students return to their seats with their index cards and cups of water. Tell the class that, unfortunately, a few of the cups were "infected" with a virus at the start of the simulation. By sharing close contact with their friends, it is likely that several more students are now "infected." Then walk around the room, placing a drop or two of phenolphthalein in each cup. Those cups with water that turns bright pink contain the "virus", so each student whose water is pink is now "infected" -- and contagious. Typically, at least two-thirds of the class will have become infected during the exchange process.

Tracking the Virus:

1. Give the students a chance to comment on the results of their experiment. They may ask who the original "infected" people were, so you should return the question to them, asking, "How can we find out?" Point out that epidemiologists are scientists and medical doctors who try to solve these kinds of puzzles, and epidemiology is a branch of medicine that is concerned with the causes, spread, and control of diseases in populations.

2. Students will likely realize they need to start by eliminating those students who were not infected at the end of the experiment, and then try to work backwards from there. Treat this as a puzzle for them to solve. Give them time to realize that they will need to get organized and devise a systematic way to look at the data they have. It may be useful to have one or two students at the board to lead the discussion and record information as they go along. Initially it may be easy to eliminate students who could not have been the initially infected ones, but it will then become more difficult. They may not be able to deduce the original three infected persons, but they should be able to eliminate all but 4-6 students.

3. Optional: At this point you can tell them that, fortunately, you took a "blood sample" from everyone before they started. If you choose not to use the test tubes for this optional step, you can just tell them which were the infected cups. Produce the rack of test tubes, and show how they are numbered to correspond to the cups that were used. Then explain that you can test for the presence of the virus using the same chemical indicator as before. Have a student volunteer put

a drop of phenolphthalein in each test tube, and students will then be able to see how close they got to determining the original sources of the virus.

Purpose: By simulating a virus being spread around the class and its subsequent tracking, students will place themselves in the role of an epidemiologist or virologist to track a virus and gain a deeper perspective on the challenges that scientists often face in this field.

Discussion Questions:

1. What percent of the class became infected after sharing close contact? What percent of the class was infected originally, before sharing close contact?

2. Why is it usually not possible to determine exactly who the originally infected persons were in a situation like this? *Usually the sources can be traced back to 4-6 possibilities, but the actual three can only be determined if all the students did their first exchanges simultaneously, then all did their second exchanges simultaneously, and finally completed the third exchanges simultaneously. Instead, during the simulation some students will have already completed their third exchanges before others completed their second. Without knowing exactly who exchanged fluids when, it is nearly impossible to determine who the original three "infected" persons were.*

3. What assumptions did we make about the virus in this tracking activity? *For instance, we assumed that we knew that the virus was spread only through close contact; what happens when it spreads more easily than that? How can we track viruses that spread in other ways?*

4. What challenges do epidemiologists face when trying to track viruses? What are some solutions to these challenges?

Activity designed by Brenna Hay, with material adapted from the University of Colorado https://www.teachengineering.org/activities/view/duk_virus_mary_act

Mary-Claire King:

Read: S. Laframboise and A. Mortazavi. "**Discovering the Breast Cancer Gene**" (article, comic and/or video). *Canada Gairdner Awards 2021 Laureates Education Materials,* pp17 - 21

Learning Objectives:

1. What is the role of DNA?

2. Describe what a gene is and how we inherit them.

3. Explain the difference between dominant and recessive alleles.

4. Name two genes that are known to be involved in the development of breast cancer.

Supplementary Reading:

DNA contains information grouped into small segments called genes. The DNA molecule contains 4 chemical bases that are represented by the first letter of its name: adenine (A), thymine (T), cytosine (C), and guanine (G), which pair up together to make DNA. A DNA molecule consists of 2 strands of bases, that are always paired together: A pairs with T, and C pairs with G. Out of convention, we only discuss the sequence of the primary DNA strand (the complementary second strand is just assumed to be paired correctly to the primary strand). The order of these bases is what specifically encodes the detailed set of instructions required to build an organism's traits. The human genome (our complete set of genetic material) contains 23 pairs of chromosomes and over 22,000 genes that are coded for by over 3 billion base pairs.

As students select each DNA Strip and tape them together in order, they are creating one chromosome containing 6 different genes that are coded for by the 4 chemical bases. This is what allows researchers to "map" the location of a gene to a specific place on a chromosome, regardless of the sequence variability itself. For example, we can "map" where the gene for hair colour is (the third gene on the chromosome), regardless of different students having different hair colours (brunette, blonde, etc.). It is the small sequence variations within each gene that lead to differences in traits. Usually, there are a limited number of sequence variations for a gene. Each form of the gene is known as an allele. In this activity, the genes have between 2 and 4 different alleles (different forms/possibilities that influence the trait). In this activity, a single gene determined each human trait. Typically, however, a trait is influenced by multiple genes as well as environmental factors.

Classroom Activity: A Recipe for Traits.
Create and decode a "DNA recipe" for a human to demonstrate how variations in DNA lead to the inheritance of different traits. Alleles for 6 genes are randomly chosen by selecting a DNA Strip out of the envelope and taped together to form a chromosome. Follow the traits key to decode the DNA and create a drawing of a person, then compare it with others to note similarities and differences.

Supplies:
- Copies of traits key (1 per student/pair)
- Drawing paper (1 per student/pair)
- Crayons or colored pencils
- Envelopes (1 per student/pair)
- Tape
- Coloured paper for preparing DNA strips (4 colours needed)

Time: 30 minutes, optional additional 15 minute activity.

Description:

Set up:

1. To prepare for this activity, make 6 copies each of DNA Strip pages A, B, C, and D on coloured paper choosing one colour for each type of DNA Strip (this will make enough for 30 student DNA envelopes). For example: 6 copies on blue of DNA Strips A, 6 copies on green of DNA Strips B, 8 copies on yellow of DNA Strips C, 6 copies on pink of DNA Strips D.
2. Cut out the DNA strips on each page (a paper cutter works well). Place 2 DNA strips of each

colour in each envelope; each envelope should contain 6 DNA strips total with 2 of each colour. Note: this is the minimum number of DNA strips per envelope needed to carry out the activity; adding more DNA strips of each colour increases the variety of possibilities for each trait.

A Recipe for Traits:

1. Students work individually or in pairs to randomly select a DNA Strip out of their envelope to determine which allele they will get for each gene.

2. Have them circle the picture for the corresponding trait after each selection and tape the strips together in order.

3. Repeat these steps for all 6 of the traits.

4. When they have finished, draw a person with all of these traits. Allow students to compare how the different people turned out.

Optional extension (15 minutes):

1. As a class, make a "map" of your human genome. Compare the different DNA recipes of each student. Point out that the gene for height is always at the top of the DNA molecule (or chromosome), the gene for hair texture is always second, and so on. Draw a representation of a chromosome having 6 segments. Have students come up with a name for each gene. Label the segments with the gene names and specify the trait they encode. Point out that although each person looks differently (has a different combination of traits), it is still possible to make a general map of the human genome. Show students a completed map of the human genome (for example, the Human Genome Landmarks Poster *https://public.ornl.gov/site/gallery/highres/GenomePoster2009.pdf*) and discuss how researchers have mapped the over 22,000 genes to particular locations on each of the 23 pairs of human chromosomes.

Purpose: This activity helps students visualize the simplified structure of DNA, from whole genome, to chromosome, to gene, and finally to individual chemical bases. By random selection of sequences, they will experience how genes can be inherited and influence corresponding traits.

Discussion Questions:

1. Are any two people alike? Everybody shares some traits in common with others, but each has an overall combination of traits that is unique. In this example, we only looked at a person using 6 genes; in reality, humans have over 22,000 genes!

2. Based on the class results, how could we calculate the probabilities of inheriting certain genes?

3. Compare how dominant and recessive traits were demonstrated in this activity (using probability of randomly selecting a DNA Strip) to how they are actually inherited (inheriting one allele from each parent).

4. Give some examples of traits that are clearly genetically inherited, and some traits that are due to environmental factors. Are there any that may be a mix of both genetics and our environment?

5. How can computers help us compile genetic information?

Activity designed by Brenna Hay with material adapted from the University of Utah https://teach.genetics.utah.edu/content/heredity/#item8

DNA STRIPS A

A T G C
A T G C
A T G C
A T G C
A T G C
A T G C
A T G C
A T G C
A T G C
A T G C

DNA STRIPS B

T A C G
T A C G
T A C G
T A C G
T A C G
T A C G
T A C G
T A C G
T A C G
T A C G

DNA STRIPS C

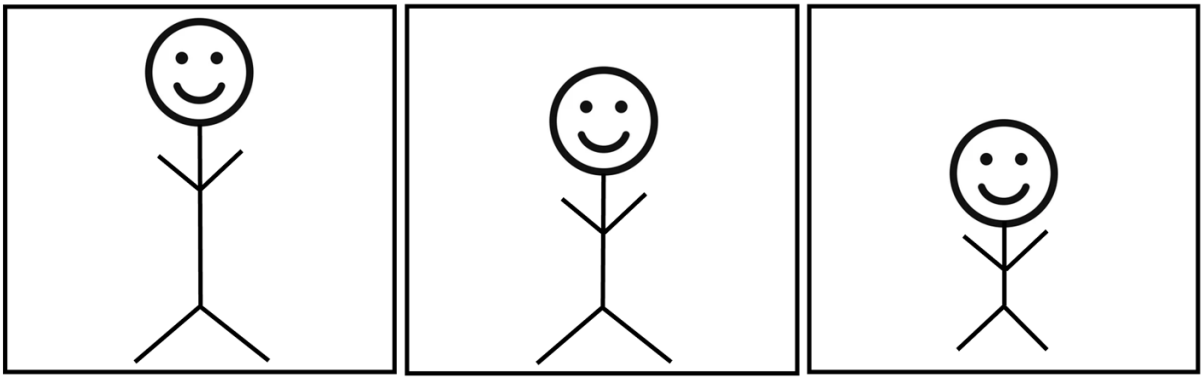
C T G A
C T G A
C T G A
C T G A
C T G A
C T G A
C T G A
C T G A
C T G A
C T G A

DNA STRIPS D

G A C T
G A C T
G A C T
G A C T
G A C T
G A C T
G A C T
G A C T
G A C T
G A C T

Traits Key

Height

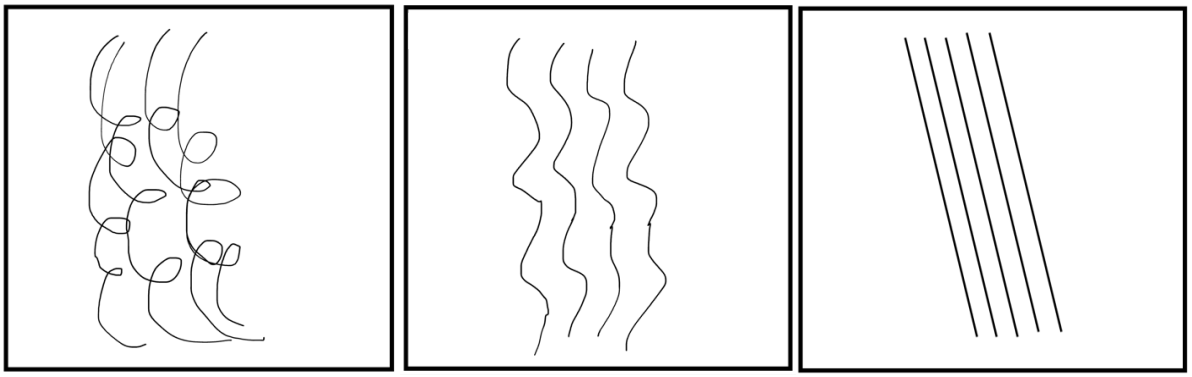


Tall
ATGC

Average
TACG or GACT

Short
CTGA

Hair Texture

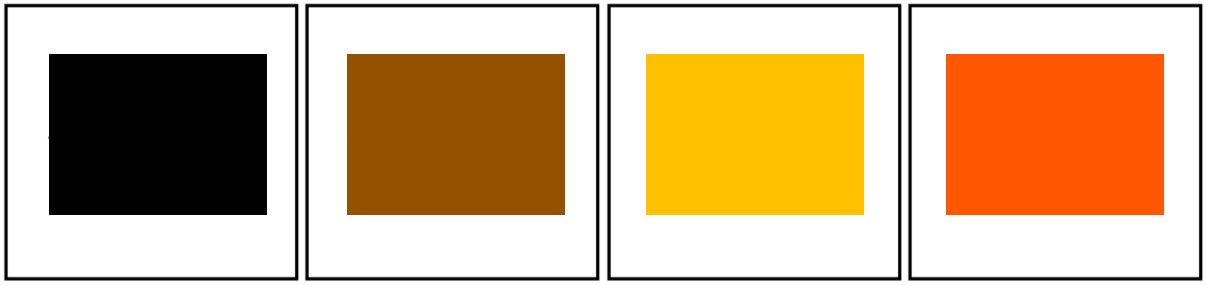


Curly
ATGC

Wavy
TACG or GACT

Straight
CTGA

Hair Colour



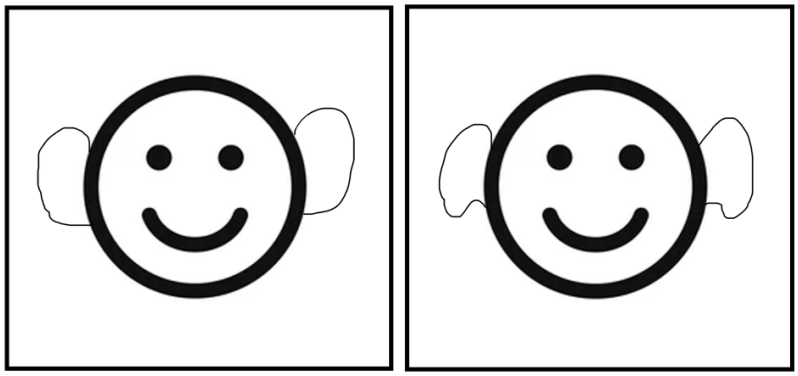
Black
ATGC

Brunette
TACG

Blonde
GACT

Red
CTGA

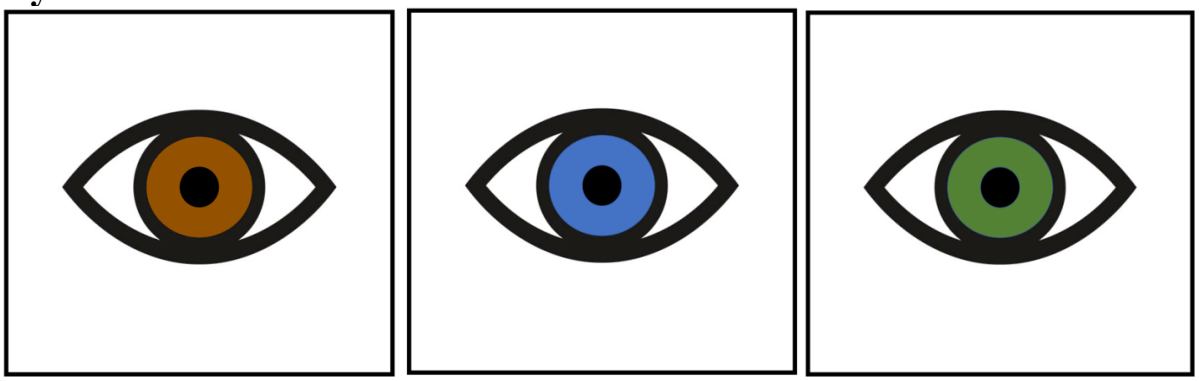
Earlobes



Attached earlobes
ATGC or TACG

Unattached earlobes
GACT or CTGA

Eyes

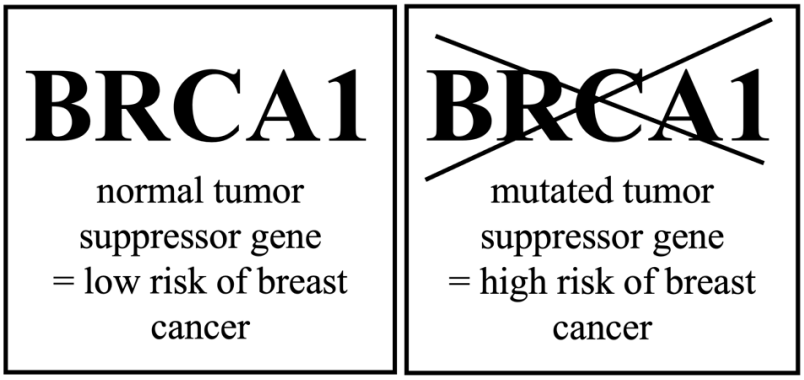


Brown eyes
ATGC or TACG

Blue eyes
GACT

Green eyes
CTGA

Breast cancer risk



Low risk of breast cancer
ATGC or TACG or GACT

High risk of breast cancer
CTGA

CONTRIBUTORS

Brenna Hay is a PhD candidate at the University of British Columbia in Vancouver, BC where she studies translation and its role in the immune response. She is passionate about teaching and leadership, especially for students in STEM fields. Brenna has mentored university and high school students and has been a teaching assistant, while also volunteering with various leadership programs and her department's graduate student association.

Sarah Laframboise is a PhD Student in Biochemistry at the University of Ottawa, where she harnesses the power of yeast to answer questions about human diseases. Sarah is a passionate science writer, graphic designer and the co-founder of the *Ottawa Science Policy Network*.

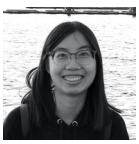
Armin Mortazavi is a Vancouver-based science cartoonist. He obtained his Bachelor's in Microbiology & Immunology from UBC and a Master of Digital Media from the Centre for Digital Media (CDM). Throughout the years, he has created illustrations and design work to educate the public about health. His past work includes an interactive graphic novel about health and wellness for the BC curriculum a course on addiction care for physicians.

David Ng is a professor, geneticist and science literacy academic at the UBC Michael Smith Laboratories. He also makes spotify playlists (@ng_dave), named after the elements of the periodic table.

Farah Qaiser is a genomics researcher by training, and also carries out policy-related research. Previously, Farah completed a Master of Science degree at the University of Toronto. She co-founded the *Toronto Science Policy Network*, leads *Wikipedia Edit-A-Thons*, and serves on the *Canada Chief Science Advisor's Youth Council*.

Zahra Sepehri received her MD from Iran. She was awarded the "Best Graduating Medical Student in Iran" in recognition of her academic, research, and extracurricular excellence. Recently she graduated from the University of Manitoba where she worked on HNF1A-AS long non-coding RNA as her masters' project. She started baking along with her studies in Canada and won first place in a competition. Thank you, Canada!

Rhonda Thygesen is currently a graduate student at the University of British Columbia in Vancouver, BC. Her work focuses on honey bee health stressors in blueberry fields. Rhonda has served as a teaching assistant and lecturer in multiple capacities as well as a mentor for highschool and undergraduate students.



Nicole Wang recently completed a Master of Science degree in the Department of Microbiology & Immunology at the University of British Columbia, where she conducted research on how bacteria protect plants from pathogens. Nicole also enjoys learning new instruments, languages, and recipes.