gairdner
LES PRIX CANADA GAIRDNER AWARDS

Canada Gairdner Awards 2022 Laureates Education Materials

(Artwork) Armin Mortazavi: (Writers) Braydon Black, Sean Vidal Edgerton, Heather Gerrie, Brenna Hay, Marie Johns, Alison McAfee, David Ng, Farah Qaiser, and Rhonda Thygesen.

TABLE OF CONTENTS

In collaboration with 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 UBC Michael Smith Laboratories, please visit https://www.msl.ubc.ca/

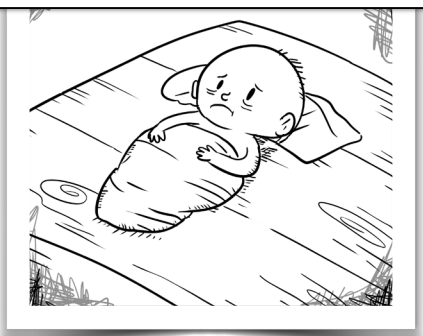
Healthy Mothers and Children make for a Healthy World

1

Pregnancy, birth, and infant development are essential moments in health. But how society functions also contributes to the well-being of mothers and their babies during this time, and research into confronting these issues and the factors which impact them is generally lacking.

2

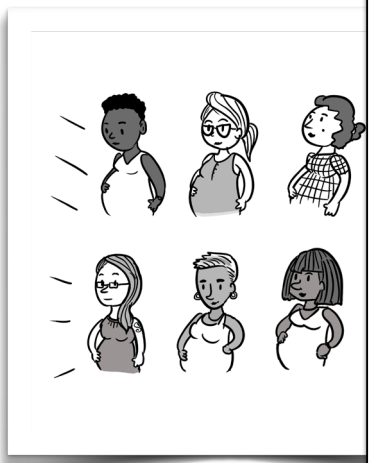
Mothers give birth to babies every day, but not all of them receive adequate medical care. Newborn survival rates are at their lowest in underdeveloped and marginalized nations where preventable conditions, such as malnutrition, are a common risk.



3

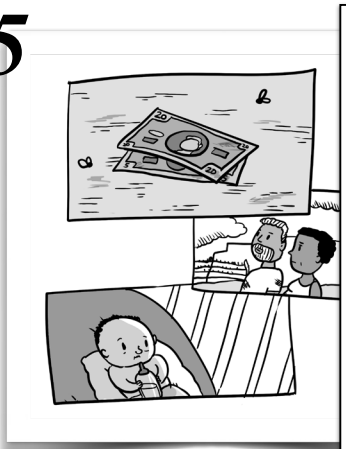
As a physician and scientist, Dr. Zulfiqar Bhutta studies methods to improve maternal-child health globally. The goal is to decrease childhood mortality as quickly as possible by treating preventable illnesses. Since Dr. Bhutta started working on the issue in the early 2000's, there has been nearly 45% less newborn deaths worldwide.

4



Dr. Bhutta has initiated collaboration with other scientists to collect data and document child and maternal health in different countries. Evidence-based interventions were then used to address specific concerns within specific populations. For example, vitamin A deficiency.

5



A large portion of Dr. Bhutta's success in newborn care and research is due to his understanding of the various injustices preventing access to healthcare such as poverty, inequity, and conflict. Much of his efforts as a doctor is spent on advocating for just global policies by promoting community intervention and independence.

6

Dr. Bhutta is currently continuing his medical research on neonatal health in the global South while acknowledging the social struggles that impact mother-child care in these communities like climate change, food shortages, and heat shocks.

Art by Armin Mortazavi and text by Rhonda Thygesen. October 2022

Healthy Mothers and Children Make for a Healthy World

Saving the lives of pregnant women and their babies relies on more than just adequate health-care.

Written by Rhonda Thygesen
Art by Armin Mortazavi

October 2022

Many of us were lucky to grow up with very few health issues. And our mothers experienced a relatively comfortable pregnancy, assured with the knowledge that medical intervention was nearby if it was needed. As babies, it was rare for our food supply to be low and if we were sick, our communities had the necessary treatments we needed. However, this is not the case in all parts of the world.

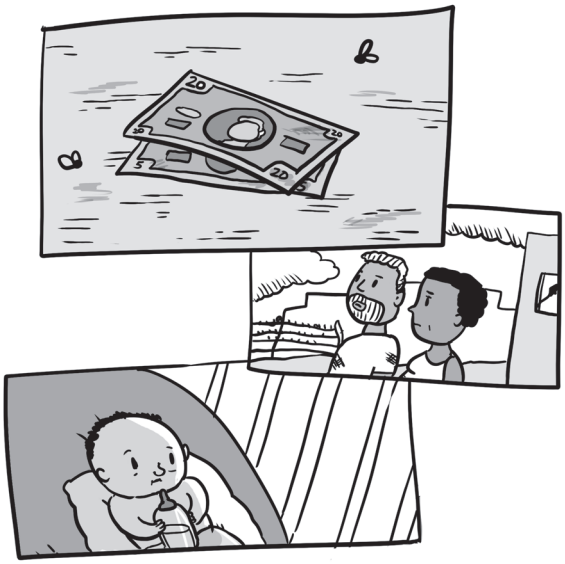
Each year, 99% of the world's maternal deaths occur in developing countries – countries where infrastructure is lacking and where poverty can be severe. For example, in Sub-Saharan Africa, 1 in 13 children die before their fifth birthday. More troubling, the majority of these deaths are entirely preventable. For example, the relatively simple act of fixing vitamin deficiencies during pregnancies would have huge beneficial outcomes. But without access to these types of specific care and resources, mothers and their neonates suffer.

Dr. Zulfiqar Bhutta is a physician and scientist studying ways to improve maternal-child health in the global context. Bhutta's medical career started in 1978 as a neonatologist in Pakistan, a country he grew up in and where he witnessed the structural conflict and poverty that was commonplace.

Neonatologists specialize in the care of newborns, but it wasn't long before Bhutta also began working with the mothers as well. Bhutta realized that he couldn't solve the health issues of the babies without considering the health of the mothers. And once he started working with the mothers, it was difficult to ignore how the **social determinants of health** impacted their well-being, and therefore their child's well-being.

Broadly speaking, the social determinants of health are the **non-medical factors** that affect health outcomes. There are many examples but a few include: racism, sexism, income, housing, food security (access to food), education, and access to health services. Depending on the situation, these determinants can have significant negative or positive effects

Understanding this, and seeing it with his own eyes in Pakistan, Bhutta's saw his responsibility as a doctor and researcher to do more than just treat the newborns in the hospital. He realized that the health of mothers and their babies was only going to improve if the inequities causing the issue were also considered.

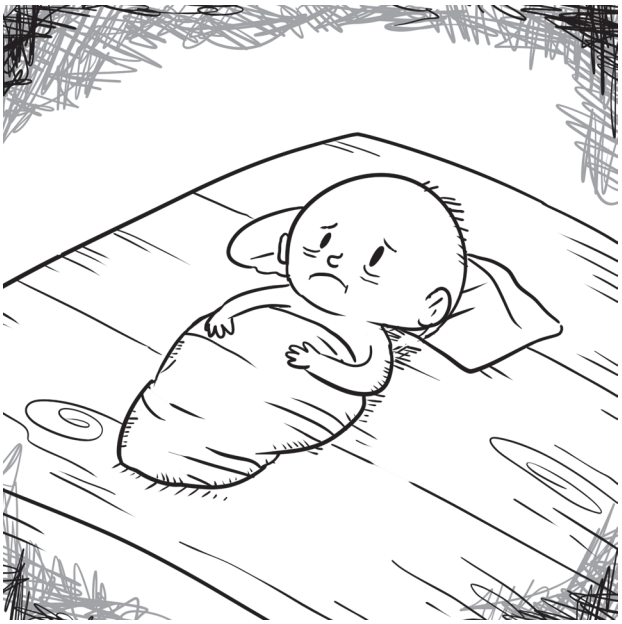


Continuing as a physician in Pakistan, Bhutta worked with colleagues in the mid-1990s to measure the impact of the Pakistani **Lady Health Workers** program. This is a program of training women (usually from the community) to be health practitioners, so that they could be on the ground to provide some health support, as well as be a more efficient connection to hospital services. Through Lady Health Workers, all mothers and children within a community would receive increased care by trained community members.

One large outcome of this work by Bhutta and his team, was the development of good practices for clean and successful home births. Furthermore, having access to Lady Health Workers, influenced women to more frequently go to the hospital for birthing, greatly increasing the overall number of hospital births - a number that has not lowered since. This research clearly showed the immediate benefits of giving women's health care more attention. However, it was also clear that there were still limits to what the community-based workers were able to do for a patient. Lady Health Workers were not fully trained physicians, and so did not have the same capabilities or resources. For example, if a woman was bleeding to death during childbirth, a health care practitioner could not help without blood stores, transfusion equipment, and the training to utilize such tools.

Bhutta explained that many of the failures in the worker model were impacted by the social determinants of health. He remembers a time where pregnant women often arrived dead at his wife's hospital even though their homes may have been only two or three kilometers away. While recounting this memory, he explained that the reasons for postponing arrival at the birthing facility were often due to inequalities in the home – for example, who held control between the sexes in the household. Furthermore, mothers and families could not always financially afford to make the trip to the hospital.

Overall, these examples emphasize how the social nuances outside the medical details of the prenatal and birthing state were both important and in need of more study. In these types of situations, Bhutta has bluntly said, "There is no medical solution."



Later, in the early 2000s, Bhutta began working on improving the health of '**the first thousand days**,' a child development term that describes the time that spans a mother's pregnancy and the life of the child until the age of two. This is the most important time for newborn development, which is also why it tends to be the time of the highest mortality.

Hypothetically, intervention at this stage could provide the greatest benefit.

Consequently, Bhutta's goal was to research real-life situations in a comprehensive manner and collect data that would hopefully reveal insight on the situation. This way, evidence-based strategies and interventions could be implemented to improve the health in underdeveloped or marginalized communities. In this context, Bhutta partnered around the globe with countries like Pakistan, Canada, and the United Kingdom to gather this data through what is called **cluster randomized effectiveness trials**. This type of research strategy analyses how groups, rather than individuals, are influenced by certain medical and social interventions, and it can be a powerful technique because it can be simpler to conduct the trails at the group level, as well as more easily allow the use of pre-existing patient data. This ultimately means that researchers may be able to receive a lot of useful information relatively quickly and with relatively little cost. Through such work, Bhutta's team discovered that the items that needed significant attention in global communities were notions like maternal-child care, diet, and age-related development.

Armed with this insight, the team then shifted their attention to using this important information to change global policies. As a strong believer in the power of advocacy, Bhutta felt that the role of a physician and researcher is incomplete, or "a job less than half done," unless you also push for the structural changes that will lead to tangible improvements.

Many examples of Bhutta's work include using evidence to strengthen the independence of community-based workers in South Asian and North Africa, and research focusing on nutrition for babies and its relation to preventable conditions such as diarrhea. In fact, the continued efforts to use data-driven science to document and change the experiences of mothers and children around the globe has influenced and set numerous international guidelines including those of the United Nation's World Health Organization.

Overall, the impact of Bhutta and his many collaborators' efforts has been immense. This strategy of using available and affordable sustainable interventions, the type that are still accessible to disadvantaged populations, has been estimated to have lowered the annual child death rate by up to 45%. The world, and mothers in particular, owe a huge thanks to Dr. Zulfiqar Bhutta's work, and for this reason, he was awarded the 2022 John Dirks Canada Gairdner Global Health Award.

Bhutta continues to work today in lower and middle income countries to improve maternal and child health. In particular, Bhutta remains attentive to current threats, such as climate change, that are impacting the lives of mothers and children in the Global South and other systemically minoritized groups.

By staying involved with global policy reforms, Bhutta hopes to discover ways to disarm the threat of climate change on impoverished citizen. In alignment with his past work, Bhutta would like to prepare those communities hit the hardest by the effects of climate change, to be more independent without the need for foreign support.

Transforming Care for the Critically Ill and the Dying

1 The hospital's sickest patients are treated by a highly trained medical team in the intensive care unit. When patients are critically ill, they are vulnerable to complications and sometimes die.

2

Dr. Deborah Cook is a medical doctor and clinical scientist who combines research science with her experience in the intensive care unit to improve care practices for critically ill and dying patients.

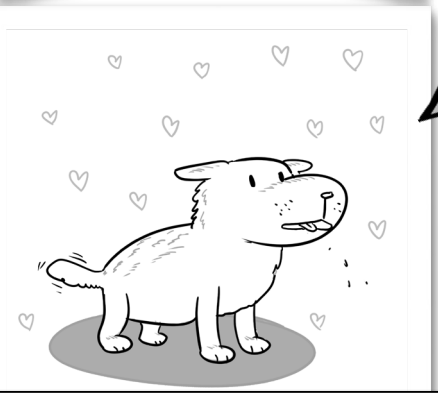
She has played a key role in research of advanced life support, prevention of complications, research ethics, and end of life care.

3

4

Unlike many scientists who focus on one specific problem, organ, or disease, Dr. Cook's research is incredibly diverse. The unifying goal of her research is to enhance the quality of life and the transition to death for critically ill patients.

5



One of her many projects is the 3 Wishes Program, which grants patients' and families' final wishes at the end of life. Wishes include having the family pet curl up on the bed or playing music during their final moments.

6

Dr. Cook has been an integral part of clinical studies that have changed the way medical teams care for critically ill patients and transformed our approach to clinical care research both in Canada and internationally.

Art by Armin Mortazavi and text by Brenna Hay. October 2022

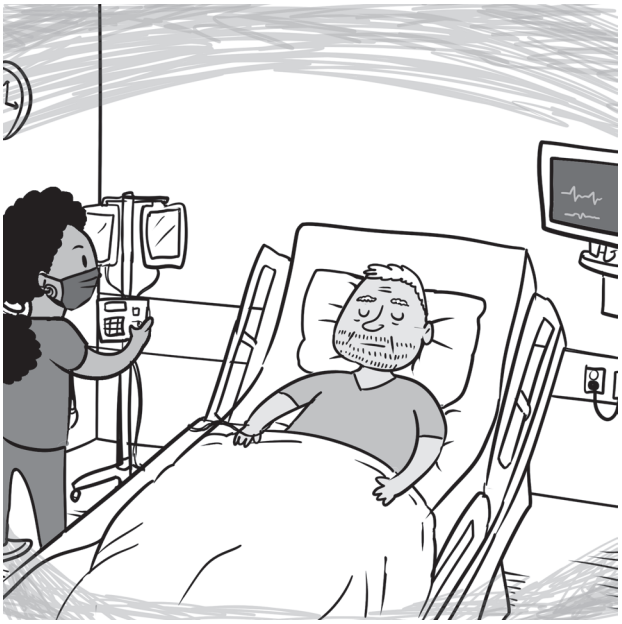
Transforming Care for the Critically Ill and the Dying

Pioneering clinical studies that have changed end of life care.

Written by Brenna Hay
Art by Armin Mortazavi

October 2022

Most people would find the pressures of the intensive care unit overwhelming: the hospital's sickest patients are vulnerable to complications and death, and patient lives are at stake. Dr. Deborah Cook, however, thrives in the intensive care unit as a clinician scientist, bringing compassionate care to patients and families every day. She takes her work a step further by teaching and performing research in the intensive care unit as well, where she translates her experience in the field to research data that is used to improve patient care.



Dr. Cook works as a clinician scientist – she is a trained medical doctor but performs scientific research as well. She brings her experience in the intensive care unit to patient-centered research to provide better care to critically ill and dying patients. This unique opportunity to perform two roles has made her both a better clinician and scientist. Although she loves her work, there are still challenges to working in the intensive care unit; it is fast-paced and dynamic, and tensions can run high given the pressures of caring for critically ill patients. Critical care patients are supported by a team made up of many different professionals; bedside nurses, respiratory therapists, physiotherapists, pharmacists, dieticians, spiritual care providers, social workers, and physicians each make up an important part of the team. Patients benefit from the ideas and expertise of a wide range of individuals with diverse perspectives, and the teamwork involved in supporting patients has made Dr. Cook's job incredibly rewarding.

Dr. Deborah Cook felt drawn to the medical field because she sees the ability to restore health as incredibly impactful. Specifically, she was interested in critical care because these patients are the sickest in the hospital. When patients are critically ill, they are more vulnerable to complications and can die. She also saw a massive knowledge gap in terms of research; while there is plenty of animal and physiology research, patient-centered research in this field is lacking. When asked about the most fulfilling part of her work, Dr. Cook immediately said that it was looking after patients, as it is "an

incredible honour to care for them at their most vulnerable."

Dr. Cook has played a key role in research of advanced life support, prevention of complications, research ethics, and end-of-life care. Unlike many scientists who focus on one specific problem, organ, or disease, Dr. Cook's research is highly multi-faceted. The unifying goal of her research is to enhance the quality of life and the transition to death for critically ill patients. She takes a two-pronged approach to supporting her patients. Firstly, she focuses on prevention of additional complications and death for patients while in the intensive care unit, and secondly, she focuses on how life support is administered or withdrawn as appropriate.

There are various methods that Dr. Cook and her team use to perform research in the intensive care unit. They use randomized clinical trials to test specific interventions against a placebo. In this type of research, some participants will be given the intervention, while others will receive a placebo, which is a substance or treatment known to have no medical effects. Another type of research she performs is observational studies. In these studies, researchers simply observe patients and collect their data in order to better understand the frequency of problems or interventions, risk factors, and consequences. Finally, Dr. Cook and her team also use surveys of practitioners, patients, and families. Survey data can be used both qualitatively and quantitatively to better understand different perspectives and get a comprehensive overview of the research topic.

Several avenues of her research include highly specific methods that improve advanced life support and reduce the likelihood of complications for intensive care unit patients. Another element of patient-centered research that Dr. Cook has investigated is research ethics. It is imperative that participation in research studies is ethical. When critically ill patients are eligible for participation in research studies, a coordinator will often need to speak to families and go through the process of obtaining informed consent. Consent must be freely given, well-informed, and is ongoing, so participants and their families can withdraw their consent to participate at any time. Dr. Cook has studied the consent process for critically ill patients and helped to determine the appropriate steps involved. Additional research ethics considerations are needed when participants are enrolled in more than one study at a time to ensure the studies will not conflict. Furthermore, Dr. Cook has highlighted the importance of a coordinated approach with the patient's clinical team, so they are providing the best care while obtaining data for the study.

Another of Dr. Cook's many endeavours is end-of-life care, which refers to the medical care and support provided in months, weeks, days, and hours surrounding death. Dr. Cook's favourite focus of teaching is end-of-life care, and she seeks to keep humanity alive amongst the technology. A substantial proportion of intensive care unit patients

don't survive, and in working with these patients, Dr. Cook had a desire to learn more about them beyond their critical illness. She ensures that the care is patient- and family-centered, and always compassionate. Dr. Cook recognizes that additional care is needed for the loved ones of the dying patient and ensuring that patients and their families receive the extra care that they need, which can include physical comfort, mental or emotional needs, spiritual needs, and practical tasks.

Her first-hand experiences working in end-of-life care led to the creation of the 3 Wishes Program, which started as a project at a single hospital and has since expanded to many hospitals internationally. This program helps to create memories and celebrate and honour the lives of dying patients through the fulfillment of small but meaningful wishes. The 3 Wishes Program has shown that it doesn't require a large financial cost or a lot of time to improve the end-of-life experience for patients and families. In fact, the mean cost of patient's participation in this project was only $27, and the impact of these actions was significant in supporting patients and families during an emotionally challenging time. Sometimes, wishes are designed to create a memory for the patient's loved ones to remember them by, such as a fingerprint keychain. Other wishes center more around creating a comfortable environment for the patient at the end of life, for instance decorating the room, bringing a bouquet of flowers, or playing music during their final moments. When asked about what some of the favourite wishes Dr. Cook had been a part of, she reiterated that it is the "simplest things that matter the most" and highlighted a wish where the family pet was brought in to curl up on the bed of the patient, and the joy and comfort that it brought them. Using surveys completed by the patients' families and members of their medical team, Dr. Cook has shown the incredible value of the program and its efficacy. The 3 Wishes Program brings together patients, their families, and medical teams to honour people's lives and bring peace to their final moments.

Another recent expansion in end-of-life care has been the increase in video technology during the COVID-19 pandemic. Compassion is at the forefront of Dr. Cook's practice in the intensive care unit, but during the COVID-19 pandemic, the ability to provide patient- and family-centered care was severely limited when visitor restrictions were imposed in hospitals. Videoconferencing technology helped to fill this gap in connection, and Dr. Cook's research into its implementation identified both drawbacks and benefits to videoconferencing technology in end-of-life care. The major drawbacks included inequitable access to technology, challenges for families setting the technology up, less authentic interactions with missed physical and non-verbal communication, and additional time required of staff. Despite these drawbacks, videoconferencing was demonstrated to be an excellent tool to support patients and families when in-person visits were limited. It was often the best option for creating moments of connection given the circumstances. Videoconferencing does bring more connection compared to other methods such as telephone calls because patients and families can still experience visual cues to connect with each other. The results of this research showed that while clinicians are hesitant to use videoconferencing technology to replace in-person interactions, it certainly plays an important role in keeping patients and families connected when in-person visits are not possible.

Dr. Deborah Cook has had an immense impact on improving patient care in intensive care units across the world throughout her career as a clinician scientist. She highlights the importance

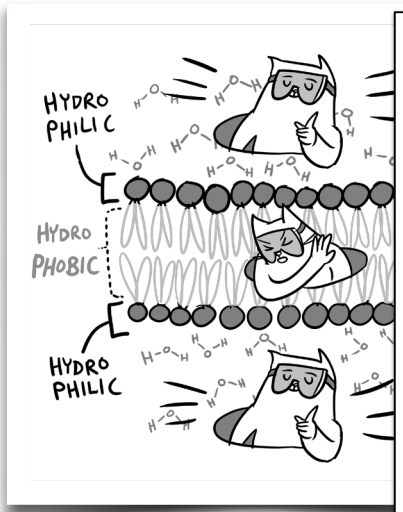
of teamwork in many of her successes. Not only is teamwork characteristic of the intensive care provided in a hospital setting, but it has also been crucial to transforming the field of critical care research. Dr. Cook praised Canada's community of researchers who prioritize collaboration ahead of competition, foster growth and leadership in early career researchers, and embrace diversity to make teams stronger. This has created a strong foundation for further research to be conducted, as the field moves towards more patient-centered large-scale clinical trials and works to fill the gap in patient-centered intensive care research. Dr. Cook has played an integral role in clinical research that has changed the way medical teams care for critically ill patients. Her efforts have transformed our approach to clinical care research both in Canada and internationally, resulting in better care and support for critically ill and dying patients.

Lipids, Nanoparticles and Beyond!

You've heard of fats – one of the primary nutrients our body needs. Well, fats are just one type of lipid – a group of biomolecules known for their inability to dissolve in water.

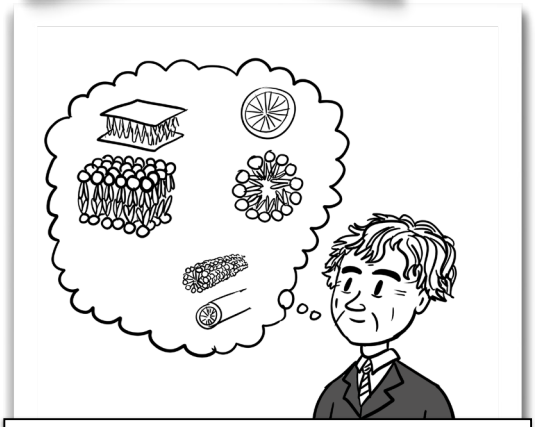
1

2



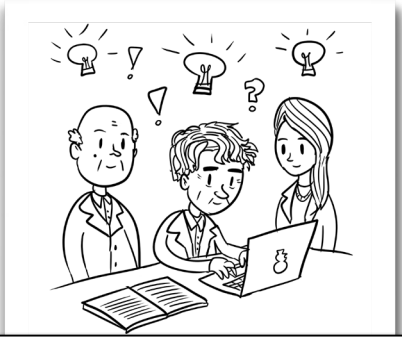
Lipids also make up biological membranes – the sacs that contain and protect cells. Because of their love-hate relationship with water, membrane lipids are typically arranged as a bilayer, with the hydrophobic ("water fearing") tail facing inwards and the hydrophilic ("water loving") head outwards.

3



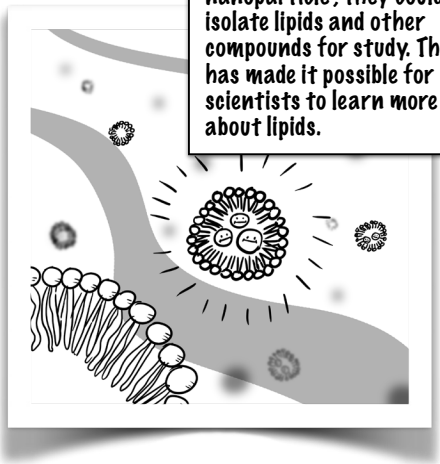
Though lipids are known for their bilayer structure, they can form all sorts of different shapes. But what drove the differences in lipid membrane shape and structure? That was the question of Dr. Pieter Cullis, physicist-turned-biochemist.

4



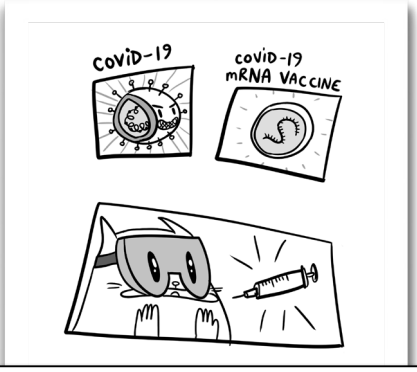
Because biological membranes have many types of lipids, they can be difficult to study. However, Dr. Cullis had a plan. He and his team would use artificial "model membranes" to isolate and characterize individual lipids.

5



By developing what they called a "lipid nanoparticle", they could isolate lipids and other compounds for study. This has made it possible for scientists to learn more about lipids.

6



As well, these lipid nanoparticles could also be used to deliver compounds into cells. One important example of this is the revolutionary work that led to the COVID-19 mRNA vaccines, changing the face of medicine forever.

Art by Armin Mortazavi and text by Braydon Black. October 2022

Lipids, Nanoparticles and Beyond!

The biochemistry of your cell membrane leads to insights that saves millions of lives.

Written by Braydon Black
Art by Armin Mortazavi

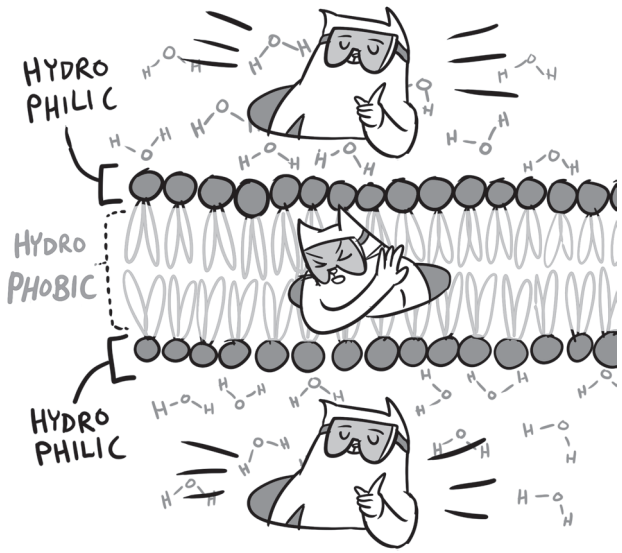
October 2022

The human body is a fascinating and complex thing. Our bodies contain trillions of cells that work together to keep us alive. These **cells**, each with their own function, are what make you *you*! They help keep you nourished and hydrated, and allow you to breathe, see, feel, and even think. Cells can do all of this, partly because they have distinct internal compartments. In other words, the inside of the cell is separated from the outside. Having this compartmentalization means that individual cells can be protected from external threats, but also that individual cells can have specific jobs.

But what are cells, anyways? And how do they function? Well, cells are a basic building block of life – think of them as tiny machines working in massive numbers that allow our bodies to work. Each cell, itself, has many parts, but the three main components for human cells include the **nucleus** (where DNA is stored), the **cytoplasm** (the fluid that fills the cell), and the **cell membrane** (the envelope that surrounds the cell and keeps it together). In particular, the cell membrane is like a good coat for the cell – it protects the good stuff inside and keeps bad stuff out. In order to do this, cell membranes need a few things, but one type of molecule in particular is especially key — **lipids**.

Lipids are a type of chemical that are defined by their inability to dissolve in water. Fats, for instance, are one type of lipid, and fats and water just don't mix (try adding oil to water to see this).

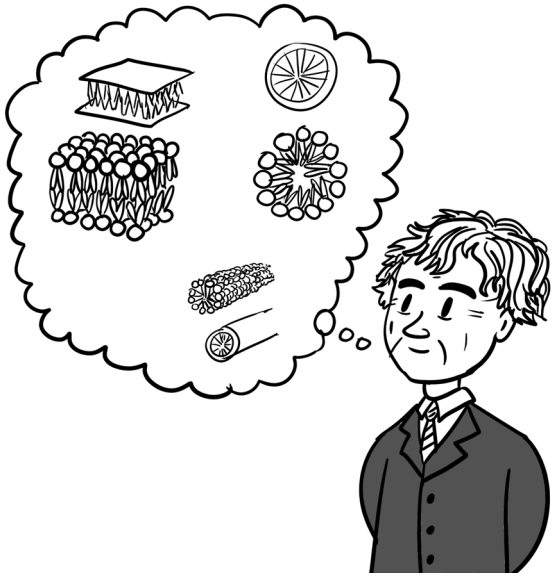
Because of their love-hate relationship with water, cells use lipids to construct cellular membranes. These lipids, many of which are called **phospholipids**, make up the cell membrane bilayer. They have a **hydrophobic** ("water fearing") tail facing inwards and the **hydrophilic** ("water loving") head facing outwards, meaning that they can interact with the aqueous or water environment inside and outside of the cell, but do not allow water or other polar substances to freely cross the membrane.



One lipid, two lipid, red lipid, blue lipid

The peculiar nature of lipid bilayers sparked the interest of Dr. Pieter Cullis, physicist-turned-biochemist. Though lipids were known to form

bilayers in water-based environments, this wasn't always the case. Lipids, he found, could form all sorts of structures, and the distribution of lipids in these membrane structures was asymmetrical – a property that was driven by the differing chemistries inside and outside of the membrane. This meant that the asymmetrical nature of membrane lipids was not necessarily random - that different types of lipids could be distributed throughout the membrane in an organized way – providing areas of a membrane that have their own set of biophysical properties and functions.



However, one major problem stood in the way – how to study the many, many types of lipids that made up the cell membrane? A cell membrane can contain thousands of different types of lipids, making it difficult to isolate and study the function of each type. But Dr. Cullis and his team had a plan. His team devised a system they called **model membranes** – a set of artificial membrane sacs (or vesicles) that could be used to isolate and control these membrane lipids for further study. By manipulating the salt environment or pH around these lipids, they found that they could generate creation of asymmetrical lipid bilayers similar to those seen in living cells.

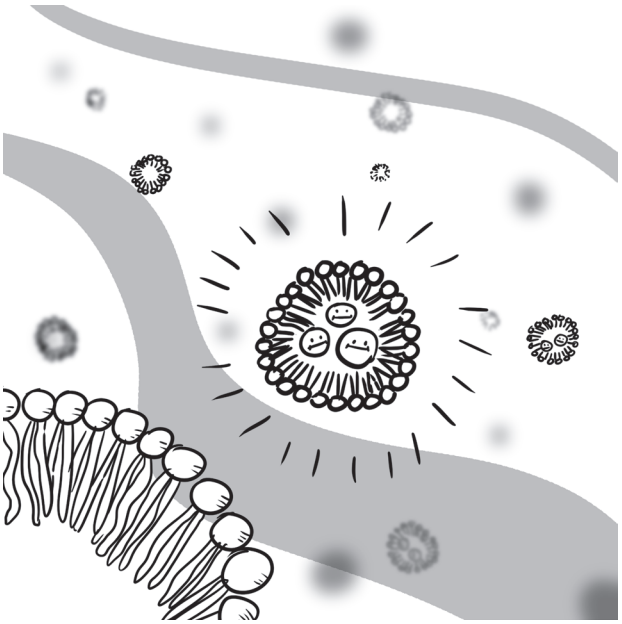
To do this, Dr. Cullis and his team developed model membranes using **ionizable cationic lipids**. These are lipids that can exist in either a neutral or positively charged form, sort of like a switch. Using these ionizable lipids was crucial to the model membrane design – it meant that the electrical charge of the membrane could be manipulated based on the physiological environment.

But why did this matter? Well, at the time it was known that cationic (or positively charged) vesicles could be taken up by cells. This concept intrigued researchers, as it provided a potential avenue to transport precious cargo (such as drugs) directly into cells. However, cationic vesicles themselves were toxic to the body making them poor candidates for drug delivery. For Dr. Cullis, there was another way. His solution was to use these ionizable cationic lipids that could remain neutral (and therefore safe) outside cells but could then become positively charged once taken up by cells. That way, lipid vesicles with targeting molecules could move through the body and bind to their target cells. They could then enter these cells and upon turning positively charged, and could release their cargo without causing harm to other parts of the body.

His idea was ground-breaking and had enormous implications for medicine and biology. This technology could enable direct targeting and delivery of compounds to different parts of the body with unprecedented precision. Cancer drugs, for example, could be packaged up and delivered directly to tumor cells, avoiding the often-harmful side effects that come with untargeted treatments like chemotherapy. Using these vesicles to package and deliver drugs offered many other advantages over traditional drug treatments. Not only could drugs be directed to avoid off-target effects – they would also be more stable during transit, have better absorption by cells, and would be less susceptible to drug resistance.

The potential of this technology – now termed the **lipid nanoparticle** (LNP) – was tremendous! Dr. Cullis saw an opportunity to bring it to medical research, and started a business centered around LNP drug delivery. At first, they focused on the targeted delivery of cancer drugs to cancerous tissue using LNPs, and their results were promising. However, business was tough – there wasn't much money to be had in delivering drugs that were already on the market. They needed something

new to put LNPs on the cutting edge of medical research.



Gene therapy and the future of medicine

It was around this time that the concept of **personalized medicine** was on the upswing. According to personalized medicine, medical treatments should consider genetic differences between individual people. Why? Well, most medicine focuses on how drugs and treatments affect broad populations – for example, the effectiveness of a drug on average for a given population. However, prescription drugs and treatments don't always work well for everyone. The reality is that each person may respond differently to the same dose of medication or may be at higher or lower chance of certain outcomes, good and bad. Because of these individual genetic differences, a "one size fits all" model can't provide everyone with the medical treatments that they need.

After starting their anticancer drug delivery business, Dr. Cullis and his team realized that the popularity of personalized medicine was taking off. And one of the next big areas of research on the horizon was **gene therapy** – a form of personalized medicine focused on treating disease by altering a person's genetic makeup. Many diseases such as cancer, cystic fibrosis, hemophilia, sickle cell anemia, and countless others have a strong genetic component, meaning that they are linked to missing or malfunctioning genes in the genome. Gene therapy offers a potential way to correct these genes by using foreign DNA (or other genetic material, such as RNA) to restore normal gene function.

However, it's very difficult to just deliver DNA or RNA to cells. The problem with introducing DNA and RNA is that they are often considered as "foreign" by the body's immune system and will be broken down in the same way that an infection might be, in order to defend the body. Luckily, the LNPs Dr. Cullis had been using are immunologically safe and could be used to transport large molecules such as DNA and RNA to the cell. This sophisticated delivery system of LNPs began to revolutionize treatment of genetic diseases. For example, the LNP-based drug *Patisiran* was developed using RNA to target mutated genes responsible for amyloidosis.

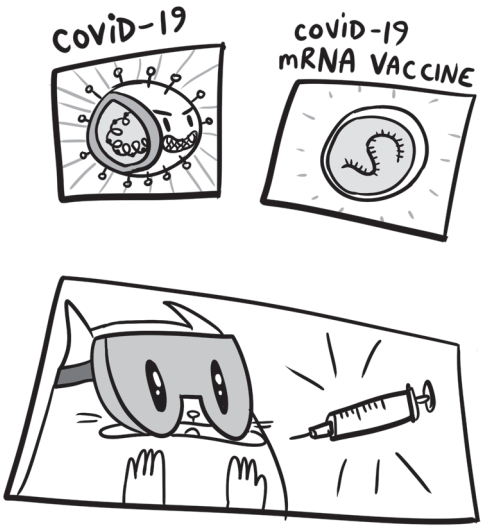
The advent of mRNA vaccines

Around the same time, Drs. Drew Wiesmann and Katalin Karikó saw the potential of LNP therapeutics for vaccine development. Until only recently, viral vaccines (such as the flu vaccine) were developed using modified or inactivated viruses and often had limitations with loading efficiency, safety, and launching an effective immune response. However, they had a novel idea – what if the mRNA blueprints for viral proteins could be packaged up and sent into our cells in the form of a vaccine? Once in our cells, the body would produce that viral protein and launch an immune response against that virus.

Clinical trials with **mRNA vaccines** against Zika virus began shortly thereafter, and the results were good. But in March 2020, the focus shifted – it was the start of the COVID-19 pandemic. Safe and effective vaccines were needed urgently around the world to stop the spread of SARS-CoV2 – the virus that causes COVID-19. Researchers had to act fast, and LNP-based mRNA vaccines were one of the answers. Today, both the Pfizer/BioNTech and Moderna vaccines for COVID-19 use LNPs to deliver viral spike protein mRNA to our cells. In doing so, our bodies can produce and recognize

this spike protein to fend off invading SARS-CoV2 that might otherwise cause serious harm.

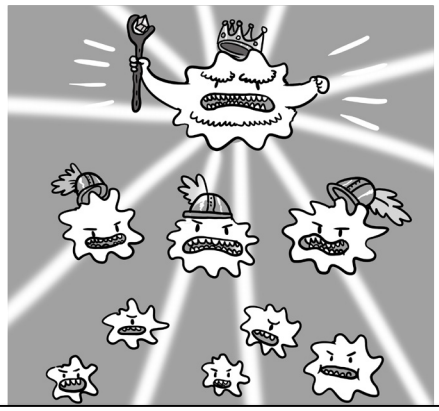
Because of the work of Drs. Cullis, LNPs have delivered mRNA vaccines to billions of arms around the world and have kept SARS-CoV2 at bay. The future of medicine has also changed. Now, researchers can develop medical treatments in a whole new way, including gene therapies that can change the lives of millions with genetic disorders.



Despite his outstanding achievements, Dr. Cullis remains humble. His advice? To remain ever curious. “If you get fascinated by something, follow the fascination, “ he says, “and don’t be afraid to change directions. Build your confidence, try new things, and learn from what you have done. Because you never know where it will take you.”

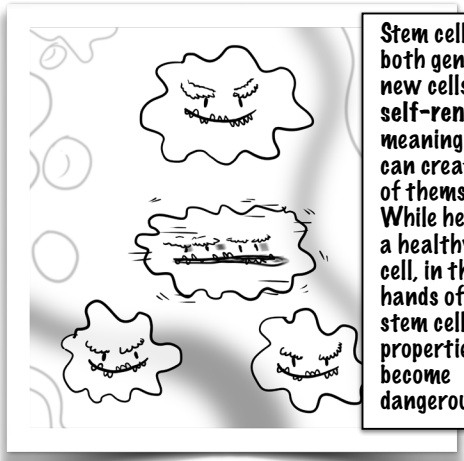
Unlocking the Mystery of Leukemic Stem Cells

1



We think of cancer as a blob-like tumor, full of generic 'bad' cells. Dr. John Dick is a scientist who discovered that not all cancer cells are equal. They are organized in a hierarchy, with a rare and powerful cell at the top - cancerous **stem cells**.

2

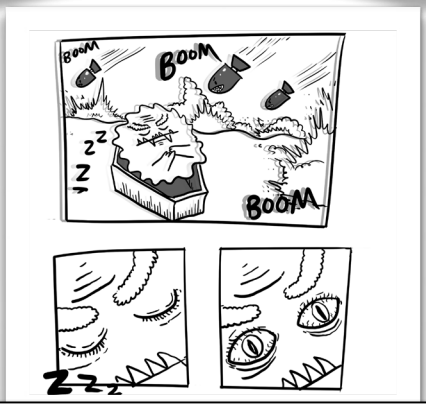


Stem cells can both generate new cells and **self-renew** - meaning they can create more of themselves. While helpful in a healthy stem cell, in the hands of a sick stem cell these properties become dangerous.

3

Dr. Dick studies **acute myeloid leukemia** (AML), an aggressive blood cancer. While patients with AML seem to respond well to chemotherapy, over half of patients relapse. But how does AML develop again so quickly?

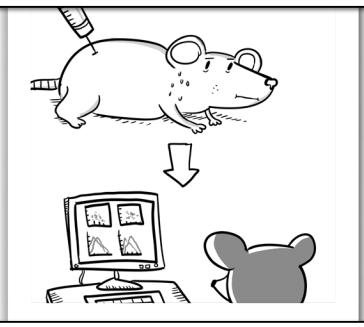
4



Dr. Dick discovered the culprit: **leukemic stem cells** (LSCs). LSCs can remain dormant for long periods of time and survive chemotherapy. After treatment, LSCs can begin generating new cancer cells and re-start the cancer growth.

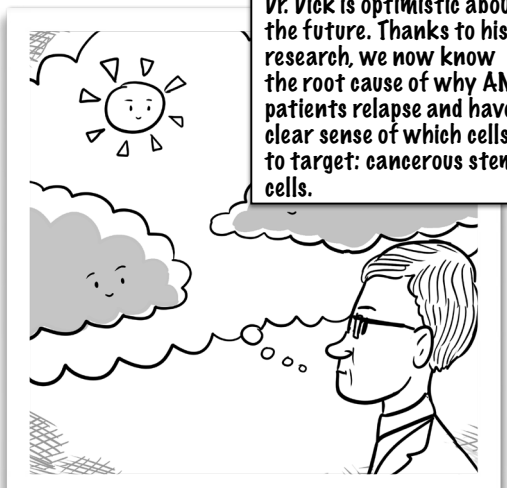
LSCs were not easy to find. Dr. Dick developed two experiments to locate this rare cell type. He first transplanted human cancer cells using a **xenograft assay** into immuno-deficient mice, to show that only a small subset of cancer cells are able to propagate leukemia.

5



Second, he used **flow cytometry** to isolate LSCs based on their unique cellular characteristics.

6



Dr. Dick is optimistic about the future. Thanks to his research, we now know the root cause of why AML patients relapse and have a clear sense of which cells to target: cancerous stem cells.

Art by Armin Mortazavi and text by Heather Gerrie. October 2022

Unlocking the Mystery of Leukemic Stem Cells

In acute myeloid leukemia, not all cells are created equal

Written by Heather Gerrie
Art by Armin Mortazavi

October 2022

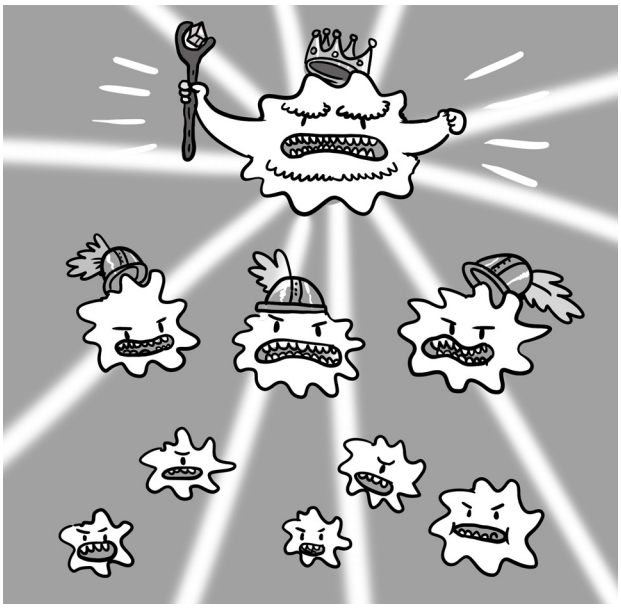
Not all cancer cells are created equal

Cancer is often thought of as a homogenous lump. A blob-like tumour full of generic 'bad' cells that expands and grows in an uncontrolled way, getting noticed and making a person sick when it begins to affect the healthy cells and tissue surrounding it. The distinction between tumour and tissue is supposed to be simple: you're either a cancer cell, or you're not. A healthy cell, or a sick cell. A good cell, or a bad cell.

For a long time, researchers thought about cancer in this way. Assuming all cancer cells within a tumour were essentially copies of the same bad cell, scientists would break down a tumour and combine the tumour cells together to study the properties of the cancer cells relative to healthy cells.

This approach to cancer research was important and led to many valuable insights into cancer genetics, metabolism, and biochemistry. A notable example is the discovery of **oncogenes** - genes capable of triggering a healthy cell to transform into a cancer cell under certain circumstances.

But there is one large oversight to this perspective. "Previous approaches to studying cancer assumed that all the cells in cancer are equal," explains Dr. John Dick, a scientist at the Princess Margaret Cancer Centre in Toronto, Ontario who has studied cancer for decades. "But what it missed was



the individual cells of that tumour, and it sort of assumed that all cells are the same."

Dr. Dick's award winning research pushed back against the assumption that cancer cells are uniform within a tumour or type of cancer. His work demonstrated that cancer cells actually organize themselves within hierarchies, with cells containing different, advantageous properties enabling them to drive cancer growth residing at the top. "Our work [...] was one of the pieces of information that really drove down the idea that only certain cells have the ability to keep that cancer going, in a way that regular cancer cells cannot" says Dr. Dick. These powerful cells are a cancerous form of stem cells, or **cancer stem cells**.

Stem cells: small but mighty

In order to understand what a cancer stem cell is, we first have to take a step back and understand the role of a healthy stem cell.

Healthy stem cells are a critical part of maintaining the body's cellular ecosystem. A small but mighty subset of cells, stem cells contain the powerful ability to generate all other types of cells. Stem cells themselves are **undifferentiated**, meaning they do not have a niche function like a skin cell or a nerve cell. Instead, stem cells spend their life producing all manner of **differentiated**, or specialized cells, needed to maintain the body's regular functioning.

After development, stem cells live in small populations throughout the body and generate new cells in an organ-specific way. For example, stem cells in the colon will continuously produce the specific cells needed to maintain the intestines. In the bone marrow, stem cells produce blood cells at a rapid rate in order to meet the high demand for new oxygen-carrying blood cells. To maintain a healthy blood supply, adult humans produce over 100 million new blood cells *per minute*. This extraordinary task is possible only by your stem cells.

Importantly, stem cells also have an enormous capacity for **self-renewal**. They possess the powerful ability to replicate and generate more of themselves. Stem cells can divide while maintaining their special undifferentiated state and therefore maintain their own population indefinitely. This property of self-renewal is an important characteristic which enables stem cells to exist in independent, self-sustaining populations.

However, imagine if a stem cell began to collect mutations over time that slowly caused them to start generating sick cells. Now the incredible ability of a stem cell to pump out the new cells needed to maintain a healthy system has turned into a factory for creating massive quantities of dysfunctional cells.

Importantly, generic cancer cells are also able to divide and replicate, and they do so rapidly. This is why chemotherapy and radiation treatments target rapidly dividing cells – their intense growth means that they take up more from their surroundings. This is also why some healthy cells that divide frequently, such as hair cells, getting caught in the crossfire. However, the rapidly dividing cells that make up the bulk of a cancer have a limited capacity for self-renew and will exhaust their ability to replicate after a finite number of divisions. It is only cancer stem cells that can continuously produce new cells and fuel long-term cancer growth.

Acute myeloid leukemia: an aggressive blood cancer

Dr. Dick's area of expertise is cancer of the blood. In Canada, over 140,000 people are currently living with blood cancer, with leukemia as one of the most common diagnoses. With leukemia, the bone marrow produces a large number of abnormal and dysfunctional blood cells - aka cancer cells. These cancerous blood cells multiply more rapidly than regular blood cells and are also less likely to die naturally, creating a recipe for the rampant spread of diseased blood cells throughout the blood system.

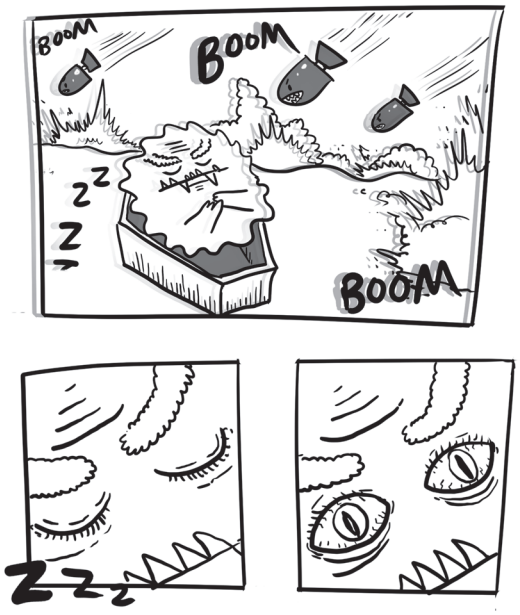
In particular, Dr. Dick studies **acute myeloid leukemia** (AML), a serious and aggressive form of leukemia which can cause a rapid decline in patients. While patients with AML often respond well to chemotherapy and the cancer seems to disappear, AML has a high rate of relapse. "80% of patients get put into remission and the disease goes away. But for the vast majority of these people, within two years the disease is back," says Dr. Dick. The five-year survival rate for patients over the age of 60 is less than 15%.

But how does a cancer which has virtually disappeared manage to regrow? Dr. Dick's laboratory

Although there are many types of stem cells, the basic idea is that they tend to be rare and special in that they have the unlimited ability to make more of themselves (self renewal), and that they are not commited to one cell type, so have the potential to become lots of different things.

was the first to solve this mystery. In AML, the culprit turned out to be a small population of dysfunctional stem cells, called **leukemic stem cells** (LSCs).

LSCs contain the perfect storm of characteristics to kickstart cancer relapse. LSCs have a slower rate of cell division than regular cancer cells and go through long periods of 'dormancy', making them resistant to traditional therapeutics like chemotherapy. In fact, not only can LSCs survive chemotherapy, they can actually become *activated* by chemotherapy. This means that while chemotherapy destroys regular cancer cells, it can cause LSCs to come out of hibernation and start producing more cancer cells again, thus triggering cancer relapse.



Finding the needle in a haystack: locating the rare LSC

Pinpointing LSCs as the culprit of AML relapse was not easy. Dr Dick's team had to develop two experiments to locate this rare type of cell and confirm that LSCs were responsible for cancer growth. The first of these experiments was a **xenograft assay**, in which human cancer cells were transplanted into immuno-deficient mice. Some of these mice would go on to develop human leukemia, while others would not. This provided a clue that it wasn't simply the presence of any cancer cell that could cause cancer to develop. A specific type of cancer cell had to be present that possessed the ability to drive cancer growth.

But these mysterious cells appeared to be quite a rare subset of the cancer cell population, vastly outnumbered by the regular cancer cells they were producing. To further isolate the culprit, Dr. Dick's lab investigated using a cell-sorting method called **flow cytometry** to differentiate LSCs from non-LSC leukemia cells based on their unique cellular characteristics. The results of these experiments showed that LSCs are extremely rare, with a frequency of approximately one out of every million leukemia cells.

These experiments, combined with further genetic analysis, enabled Dr. Dick's team to map out the complex evolutionary pathway of LSCs. "You need a sequence of events to happen before you actually get a full cancer," says Dr. Dick, "Cancer doesn't happen overnight. One normal cell picks up a mutation that makes it just a little bit more advantageous. That cell expands a little bit more, picks up another mutation, and so forth." His team tracked how normal blood stem cells develop into pre-leukemic stem cells, and then eventually become mature LSCs. The point at which LSCs become capable of generating AML can occur up to a decade after the first healthy stem cell begins mutating. Further genetic analysis enabled Dr. Dick to develop a 'stemness score' that uses 17-genetic markers to predict therapy outcome in AML patients.

Cancer and optimism: the future of cancer treatment

Despite the difficulties of cancer research, Dr. Dick finds the future of AML to be filled with hope. Thanks to Dr. Dick's team, we now understand why patients with AML are so prone to relapse and have a better idea of which cells to target moving forward.

This key piece of information also comes at a time when rapid advances in scientific technology and gene therapy are changing the odds for the better when we face cancer. "Technology is just coming together on a massive scale," says Dr. Dick, "The

idea that what used to require 100 billion cells to get insight into genetics, we can now do with a single cell is remarkable. So we can quickly sift through single cells of a normal tissue or leukemia or any cancer and begin to ask, 'what are that particular cancer's vulnerabilities'?"

The stemness score that Dr. Dick developed for AML also helps guide therapeutic choice by determining the particular genetic makeup of a patient and their cancer. "Now we can begin to tailor therapies based on not just an individual patient, but the individual cells that have particular vulnerabilities," says Dr. Dick, "So that gives me huge optimism for the pace of advances that we're going to undertake."

Dr. Dick's optimism provides confidence that the outcome for patients with AML is improving. With a clear idea of what we're facing, we know which cells to target for future cancer treatments: leukemic stem cells.

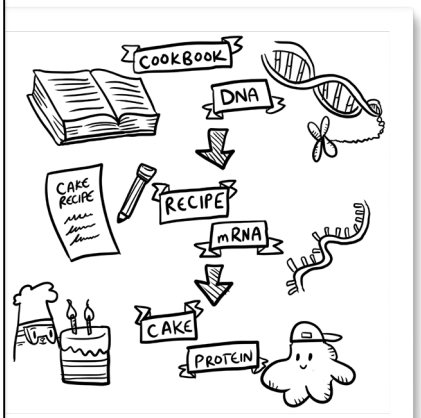
mRNA: from instability to a world-changing vaccine

1

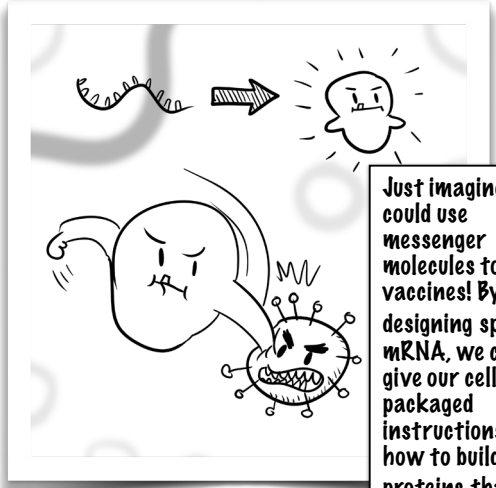
In our cells, proteins are the molecules that actually build things: like keratin in our fingernails, or antibodies to fight viruses. Similar to how you would use a recipe to bake a cake, our cells rely on the instructions found in DNA to build these proteins.

2

When our cells are ready to make a protein, parts of our DNA are copied into a messenger RNA (mRNA) molecule. The mRNA will carry this recipe to a ribosome (a chef), which will then build the specific protein.

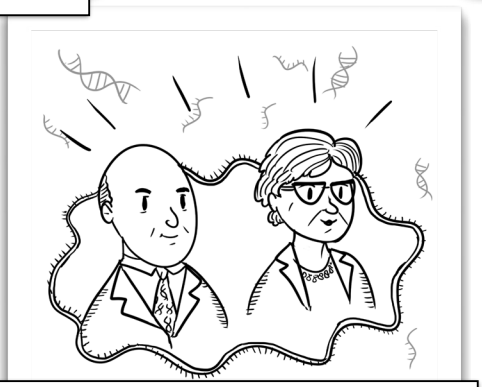


3



Just imagine: we could use messenger molecules to build vaccines! By designing specific mRNA, we can give our cells pre-packaged instructions on how to build proteins that can help us fight different viruses.

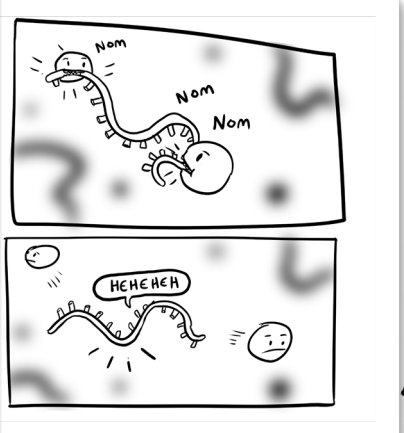
4

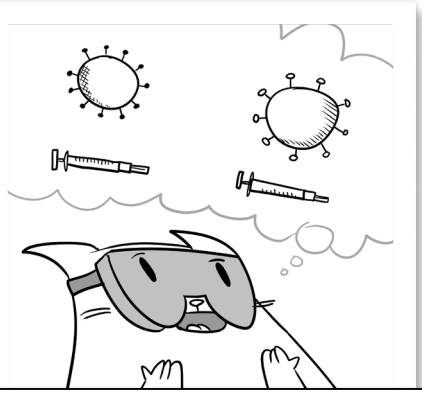


But it isn't easy to work with mRNA, as it is unstable and breaks down quickly. These are some of the challenges that Dr. Katalin Karikó and Dr. Drew Weissman have been working tirelessly to address for the past few decades.

5

Karikó and Weissman engineered mRNA to protect it from being broken down quickly. This meant that mRNA could be successfully delivered into human cells, to produce specific proteins. This was ground-breaking!





6

During the COVID-19 pandemic, researchers at companies like Pfizer/BioNTech and Moderna, used this work to quickly develop safe and effective COVID-19 mRNA vaccines, and protect us all from becoming seriously ill. Now, scientists are beginning to build and test mRNA vaccines against other threats, like influenza and HIV.

Art by Armin Mortazavi and text by Farah Qaiser. October 2022

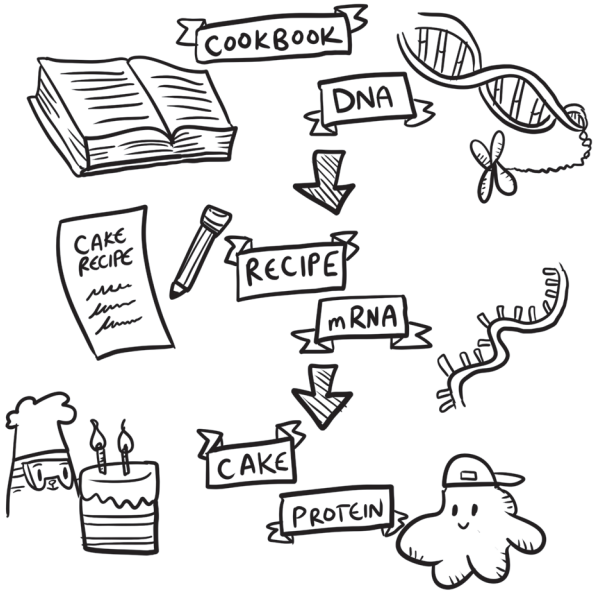
mRNA: From Instability to a World Changing Vaccine

Imagining messenger molecules that can build vaccines.

Written by Farah Qaiser
Art by Armin Mortazavi

October 2022

With a set of instructions in hand, you could make a cup of tea, bake a mouth-watering cake, or even make appetizers, dinner and dessert for your friends and family. Similarly, the cells in our body use instructions found in DNA, our genetic code, to build over tens of thousands of proteins. Together, these proteins carry out different functions in our body, from the keratin which protect our fingernails, to the hemoglobin carrying oxygen in our red blood cells.



When our cells want to make a protein, they first carry out **transcription**, by copying instructions from DNA into **messenger RNA** (mRNA). These mRNA molecules are special because they are mobile and can carry the instructions to a ribosome (a protein chef), which will then build the specific protein, in a process called **translation**.

Just imagine: by designing specific mRNA, we can give our cells pre-packaged instructions on how to build any protein. This opens up a world of endless possibilities!

Sadly, it isn't easy to work with mRNA, as it is unstable and breaks down quickly. These are some of the challenges that countless scientists, including Dr. Katalin Karikó and Dr. Drew Weissman, have been working tirelessly to address for the past few decades.

In 1985, Karikó, a Hungarian biochemist with a doctorate in biochemistry, emigrated with her family to the United States, and later started working at the University of Pennsylvania. She was single-mindedly researching mRNA, for its potential applications in heart disease and stroke, convinced that it could be used to develop therapies and treatments.

Like many scientists, Karikó wrote several proposals to granting agencies, requesting funding to support her mRNA research. But Karikó's research proposals were rejected, again and again. She was

forced to move from lab to lab in search for stable funding for her research. In 1995, Karikó had to accept a demotion, and a pay cut, all to continue her mRNA research at the University of Pennsylvania.

"When I told people that I worked with mRNA, they felt sorry for me," says Karikó. "But I could see progress in my work."

In 1997, Weissman, a physician-scientist with expertise in immunology and microbiology, joined the University of Pennsylvania and started a new lab. He wanted to make a better vaccine, and fight diseases like HIV.

Soon, Weissman and Karikó met in an unlikely encounter at the photocopier machine in the hallway. "We both read a lot, so we would fight over the copy machine. Back then, that was the only way to read an article," says Weissman.

"If technology had been more advanced, I would never have met Drew Weissman," says Karikó, laughing.

"We started talking," says Weissman. "She was interested in what I did. I was interested in what she did. We started working together."

Karikó and Weissman started collaborating to develop an mRNA-based vaccine, beginning a partnership that has lasted for more than two decades. In some of their early work, the duo found that injecting synthetic mRNA into immune cells triggered widespread inflammation.

Why was this happening? What Karikó and Weissman needed was a way to stop the immune system from identifying the synthetic mRNA as a foreign pathogen, and instead, convince the cells that this was an mRNA molecule to transcribe and translate into a protein.

It took many years, but in 2005, Karikó and Weissman were finally successful. The two scientists were able to chemically modify mRNA – specifically, by making a simple chemical tweak to the building blocks of mRNA, where they replaced the nucleic acid uridine with **pseudouridine**. This protected the synthetic mRNA from being broken down quickly, and allowed it to slip past the body's immune defenses. Now, the synthetic mRNA could be used by cells to produce specific proteins, without triggering inflammation. This was a game-changer.

Thanks to Karikó and Weissman, it was now possible to design mRNA to produce proteins to fight different viruses, such as HIV and the flu. It was revolutionary, because traditional vaccines will deliver a dead or weakened virus to stimulate the immune system and teach the body how to fight an infection. But with mRNA, the body's own cells could produce a carefully chosen viral protein and simulate an immune response, without posing any risk of infection.

Karikó and Weissman were excited and braced for interest from the scientific community.

"In our minds, we had solved the problem of RNA therapy," says Weissman. "It had been in clinical trials and failed. Everyone had given up on it. We thought we figured out how to overcome that. I told [Katalin Karikó] that the next morning, our phone would be ringing off the hook with people wanting to use our method to deliver mRNA."

But at the time, few scientists recognized the importance of this discovery, let alone the broader public.

"Of course, nobody called us," says Karikó. "So, we focused on things which we could still see needed to be solved."

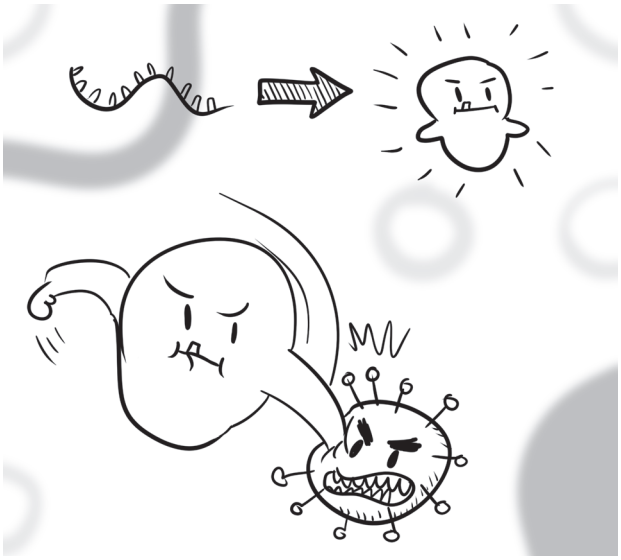
Disappointed, but undeterred, Karikó and Weissman continued their work to better understand mRNA. They applied for, and received, patents, and even founded a small company. Karikó went on to work at an RNA pharmaceutical company, called BioNTech, in Germany.

All of this changed when the COVID-19 pandemic hit the globe. The first COVID-19 cases were reported in late 2019, but it wasn't until January 2020 that the sequence for SARS-CoV-2, the virus which causes COVID-19, was uploaded online. It only took days for researchers in academic institutions and pharmaceutical companies, like Pfizer/BioNTech and Moderna, to use these viral sequences and generate potential mRNA vaccine candidates to test in both cells and animal models, and later, in human clinical trials.

Specifically, researchers used Karikó and Weissman's discovery to synthesise COVID-19 mRNA vaccines which contained the code to the 'spike' protein that the virus SARS-CoV-2 uses to enter cells. By delivering these instructions via the COVID-19 mRNA vaccine, our cells could now recognize the virus and learn how to fight it off. Still, despite this approach, the vaccines also needed a transport system that could safely deliver this synthetic mRNA into human cells. Researchers decided to use lipid nanoparticles, developed in part by Dr. Pieter Cullis' laboratory at the University of British Columbia. Essentially, these are tiny protective bubbles of fat, which protect the mRNA and deliver it into target cells. Together, Karikó and Weissman's discovery, and Cullis' lipid nanoparticles, meant that researchers were able to quickly develop safe and effective COVID-19 mRNA vaccines.

To say that the COVID-19 mRNA vaccines were ground-breaking is an understatement. The first COVID-19 mRNA vaccine, outside of a clinical trial, was administered in December 2020. This lightning speed was only possible thanks to the many earlier decades of research into mRNA.

Almost two years later, over 700 million doses of the COVID-19 mRNA vaccines have been administered. These mRNA vaccines have changed the course of the pandemic, decreasing the likelihood of serious illness, hospitalization, and death.



"I never imagined a pandemic like this," says Weissman. "I had thought [our research] would probably have been used in a vaccine, maybe during a pandemic, but more likely in an influenza [outbreak], like the one we had in 2009. The COVID-19 pandemic was unprecedented."

In recognition of their extraordinary impact, Karikó and Weissman were awarded a Canada Gairdner International Award in 2022. Their pioneering work in developing modified mRNA – one of the foundational technologies necessary for developing safe and effective COVID-19 mRNA vaccines – continues to have far-reaching impacts today.

As a young child, Weissman would take everything apart, from doorknobs to toasters. "I wanted to see how things worked," said Weissman, reflecting on his childhood. "For a youngster thinking about science, I think the important things are creativity and curiosity."

Now, Weissman's lab is working on over 20 other vaccines for various diseases, from malaria, tuberculosis to HIV. Several of these vaccine candidates are in human clinical trials. Weissman is also deeply focused on ensuring that everyone, not just those living in wealthier countries, have access

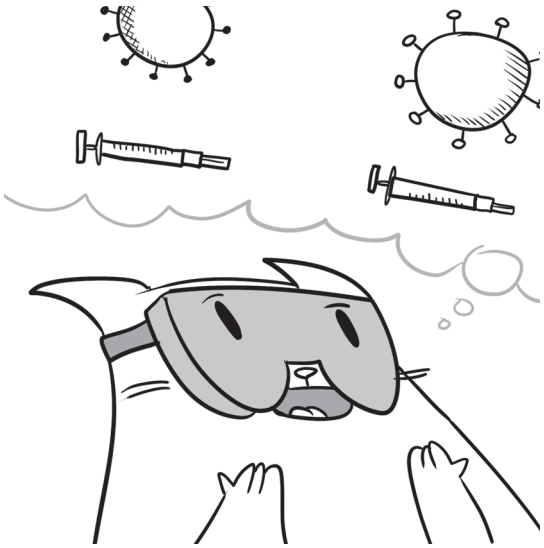
to mRNA vaccines. He is working with several countries, including Thailand, Rwanda, and South Africa, to develop and test affordable COVID vaccines.

“The idea was that we wanted local production of vaccine, so you’d have local delivery,” says Weissman. “That means both making the vaccine there, but also having the scientists there who design the vaccine, and the next vaccine after COVID.”

“I’m happy back in my lab, working,” adds Weissman, noting that the attention from his research has taken some time to get used to. The attention has ranged from requests for autographs from strangers on the street, and sadly, death threats too.

Karikó is now a senior vice president at the pharmaceutical company BioNTech. She uses interviews as an opportunity to showcase scientists in the public sphere, speak about the importance of vaccines, and encourage the next generation of scientists to be confident and believe in themselves.

“You have to believe,” says Karikó, and refers to how she, as a butcher’s daughter in Hungary, ended up at an Ivy League school. “You have to believe, no matter where you come from.”

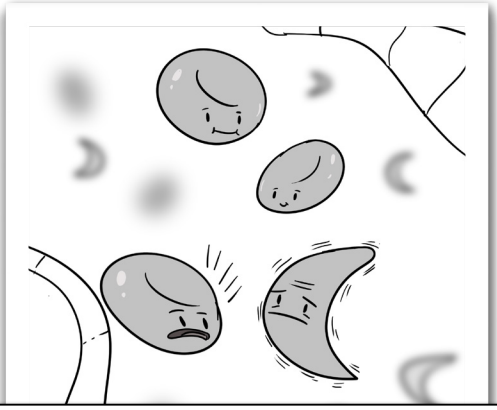


This scientific story is an excellent example of how much work and time is involved in making scientific discoveries. People tend to think the science of COVID mRNA vaccines was rushed, but in reality, several decades of research was necessary to get to the finished line!

Sickle Cells and a Tale of Two Hemoglobins

1 About 100,000 Americans and 5,000 Canadians are living with sickle cell disease – a severe blood disorder caused by defective hemoglobin, a crucial protein responsible for carrying oxygen.

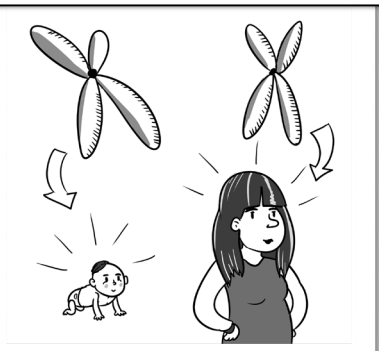
2

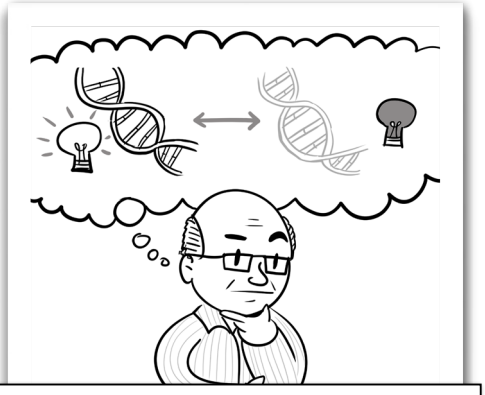


Normally, red blood cells are shaped like a donut, but the defective hemoglobin gives the cells a sickle shape, like a crescent moon. These sickle cells are stiff, sticky, and have a very short lifetime.

But humans have more than one hemoglobin gene – one is produced in developing fetuses, and after birth, babies quickly switch to the adult version. It's only mutations in parts of the adult version that causes the disease.

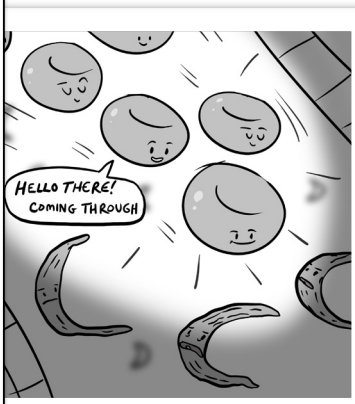
3

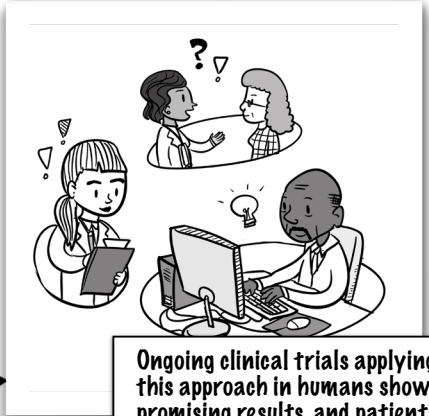




4 When Stuart Orkin discovered the molecular switch that normally turns off fetal hemoglobin production in babies, he saw an opportunity to turn this into a new treatment.

5 Orkin knew that by turning fetal hemoglobin back on, the healthy fetal version could replace the dysfunctional adult version and cure the disease. And now that he had identified the switch, he could manipulate it.





6 Ongoing clinical trials applying this approach in humans show promising results, and patients could soon be liberated from this debilitating disease

Art by Armin Mortazavi and text by Alison McAfee. October 2022

Sickle Cells and a Tale of Two Hemoglobins

A molecular switch is discovered that could lead to cures for many blood diseases.

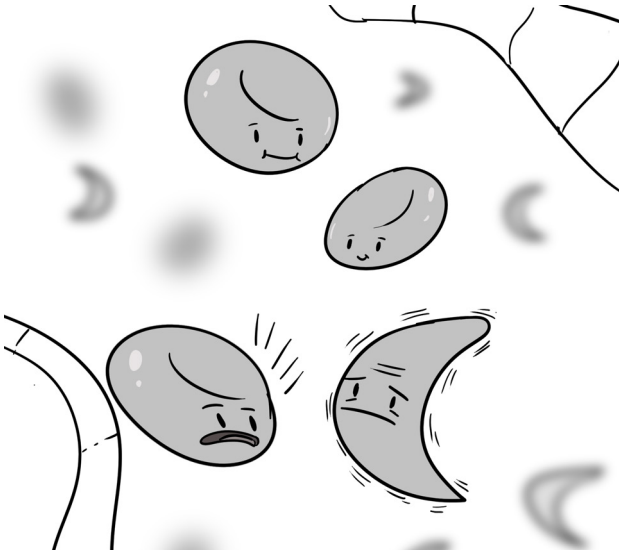
Written by Alison McAfee
Art by Armin Mortazavi

October 2022

Imagine being so familiar with the hospital that it feels like a second home – a home full of painful memories, tests, and bad news. You are scared of simple things, like swimming, because the shock of the cold water might send your body into an episode of the worst pain you have ever felt, lasting for days. You are constantly worried that you might get sick, and even a common cold could land you back in the hospital. None of this is a surprise, because since you were a youngster, you have been told that your life would probably be thirty years shorter than your peers and full of hospitalizations.

That is what it's like to live with **sickle cell disease**, an illness that affects about 5,000 Canadians and 75,000-100,000 Americans. Worldwide, the condition is most prevalent in people living in the so-called "malaria belt" – countries located in Central and South America, Sub-Saharan Africa, as well as South and Southeast Asia – with about 300,000 people born with the condition each year. But today, there is real hope for the many patients afflicted. New research by Stuart Orkin has laid the foundation for a suite of new therapeutic options. For this, Dr. Orkin has been recognized by a Canada Gairdner International Award in 2022.

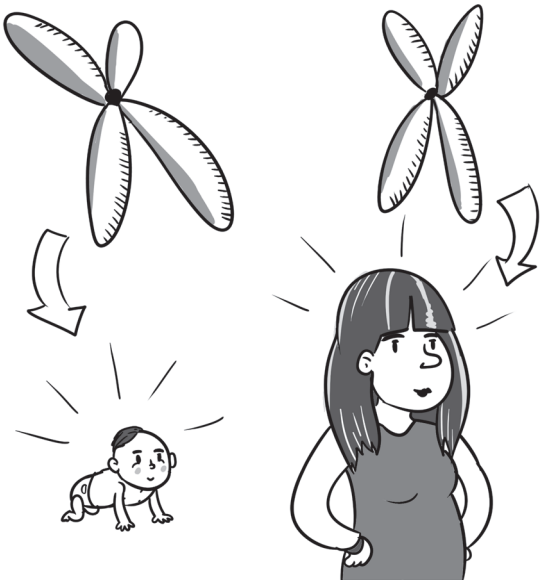
"**Hemoglobin** carries oxygen," says Orkin, the David G. Nathan professor of pediatrics at Harvard Medical School. "That's its main function, to carry oxygen and deliver it to the tissues." Hemoglobin is made up of not one protein, but two pairs of two different proteins known as the alpha and beta subunits. Sickle cell disease is caused by a single mistake, or mutation, in the beta subunits, which causes developing red blood cells to produce hemoglobin that is the wrong shape. This makes it glob together, or polymerize, inside the cells, turning them into the shape of a crescent moon instead of the normal squishy donut.



When the hemoglobin sticks together like this, it is not as good at binding to the oxygen. Even worse, the abnormal shape of the cells means that they are more likely to clog blood vessels, leading to painful episodes and other serious complications.

Luckily, humans have multiple types of hemoglobin which are normally produced at different

stages of development – embryonic, fetal, and adult hemoglobin – and it is only the mutations in components of the adult version that causes sickle cell disease. Similarly, a related disease called **beta-thalassemia** occurs when cells can't produce enough of one of the adult hemoglobin subunits.



Both of these diseases could be cured by using fetal hemoglobin as a stand-in, if only we knew how to make cells switch over to making it. Orkin, who has dedicated his career to studying diseases of the blood, discovered just that, which has led to several promising therapies.

Orkin describes his work as "solving a biological problem that has been out there for fifty years." Scientists and doctors have known about the different types of hemoglobin for a long time; indeed, as early as the 1940s, Janet Watson, a pediatric doctor in New York, noticed that very few children who later developed sickle cell disease were hospitalized as babies. She knew that, like all mammals, humans produce a different kind of hemoglobin as a fetus than as an adult, and that it takes some time after birth for the fetal version to be completely replaced – around when she would start to observe symptoms in her patients.

At a time when the exact cause of sickle cell disease was not yet known, Watson already suggested that perhaps newborns were protected from the disease because they still had their healthy fetal hemoglobin circulating in their blood. "The paucity of cases in infancy is surprising in view of the frequency of hospital admissions later in childhood," Watson wrote in 1948. "It seems likely, then, that fetal hemoglobin lacks the sickling properties of adult hemoglobin, thereby … partially protecting the infant in the first four months of life."

Later, Linus Pauling would famously describe that mutated adult hemoglobin was indeed what causes the disease, and Watson would be proven right. To astute clinicians like Watson, Orkin says, "we owe a huge debt."

But exactly how developing red blood cells switch from producing fetal hemoglobin to adult hemoglobin wouldn't be deciphered for decades. Soon after scientists invented the technology to sequence whole genomes – our complete genetic code – and scan those sequences to find relationships between genes and diseases, Orkin and his team applied that approach to look for a gene that might be responsible for the fetal-to-adult hemoglobin switch.

In a case of what Orkin describes as "dumb luck," his team and other researchers identified one gene, a lynch pin, that appeared to play a big role in how much fetal hemoglobin a person was able to produce. That gene, called ***BCL11A***, encodes what's known as a transcription factor, a type of protein that regulates gene expression, often in complex ways. Importantly, the researchers were able to show that by manipulating this specific gene in mice, they could adjust the amount of fetal hemoglobin produced, even in adult mice.

"We didn't know how many factors would be involved in the switch," Orkin says. "We thought there would be many factors with a complicated mechanism, but in mice, all we needed to do was get rid of *BCL11A* to reactivate the fetal form of hemoglobin and cure their sickle cell disease. That

Why would a human need two versions of the hemoglobin? The reason for having multiple versions, they think, is because a developing fetus needs to extract oxygen from the mother's blood, and so requires a hemoglobin that binds more strongly to oxygen.

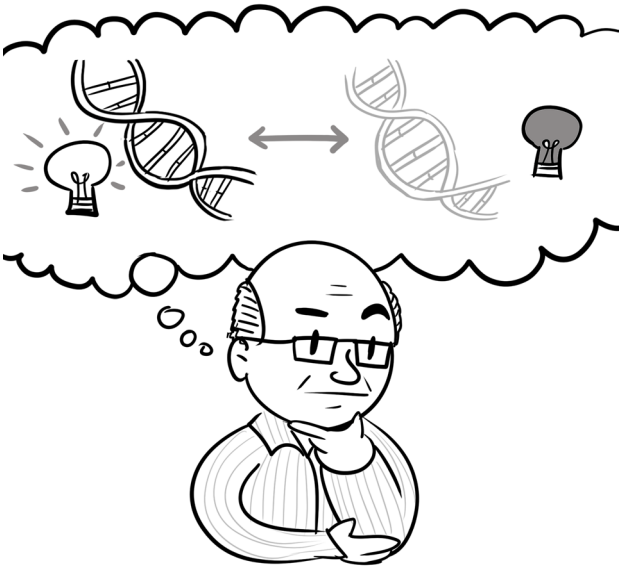
experiment showed us that if we could do something similar in a human, we would essentially have a cure."

And a new cure, we may soon have. Two companies, Vertex Pharmaceuticals and CRISPR Therapeutics, are collaborating to develop and commercialize a new therapy, based on Orkin's discoveries, that could be a huge improvement over bone marrow transplants. The companies have publicly announced that they are aiming for approval by the Food and Drug Administration by the end of 2022.

Currently, a patient with sickle cell disease can be cured by getting new blood stem cells – the cells within bone marrow that give rise to different types of blood cells, including red blood cells – and until recently, the only way to do this was to have a bone marrow transplant from a healthy donor. But this is an extremely invasive procedure, and that's only if a patient is lucky enough to find a donor with stem cells similar enough to their own for a transplant to be accepted. For most patients, the likelihood of finding a match is about one in ten.

But today, thanks to biotechnology, we now have the capability to extract stem cells from a patient with sickle cell disease, edit the *BCL11A* gene to turn back on fetal hemoglobin production, and give the cells back to the patient. This approach, which is an example of what's known as "gene therapy," greatly improves the probability that the cells will be accepted, since they came from the patient in the first place. The red blood cells that arise from the edited stem cells will have a healthy, normal shape, freeing the patient from disease.

One worry for any gene therapy is that artificially manipulating our genes might cause unexpected problems. But, before gene therapy trials for inducing fetal hemoglobin even began, nature answered that question for us: some rare people naturally keep producing fetal hemoglobin throughout their life, and they have no problematic conditions. Even a woman producing fetal hemoglobin as an adult is able to successfully carry a baby to term.



Vertex Pharmaceuticals and CRISPR Therapeutics have now treated over 70 patients with sickle cell disease or beta-thalassemia using their gene editing approach. This method is so successful in part because the editing does not have to be completely efficient – even partially turning on fetal hemoglobin is sufficient to prevent the sickling process and avoid the worst symptoms of the disease. However, the expected cost of such a therapy is astounding.

Though this service not yet commercialized, the price tag on a similar therapy, also expected to be approved for use in the US in 2022, is estimated to be in the range of $1-2 million USD. It might sound shocking, but Orkin thinks this isn't a crazy figure. "Economically, it's a good value. With the cost of care for affected people, their poor quality of life, lost wages, shorter lives, and lost productivity, $2 million is probably a bargain."

Rich countries will probably help pay for such a therapy, but the countries where the vast majority of patients with sickle cell disease live will not likely be able to afford it. Still, cheaper therapies could soon be on the horizon.

While extracting and editing stem cells has been the preferred gene therapy avenue because it enables tight control over which cells are modified, another potentially less invasive option would be to inject a patient with a gene editing formulation directly into their bone marrow. However, a worry

about such a systemic, injectable approach is that it is very hard to control which cells get edited, and editing the wrong ones could cause complications in other organs or tissues.

Fortunately, that's not a problem for *BCL11A*. There is one part of the *BCL11A* gene that specifically controls its production within developing red blood cells, and not elsewhere in the body, where it likely conducts other important jobs. Because of this, no matter which cells are edited, only the blood stem cells – and subsequently, the red blood cells – will see an effect.

The challenge, though, is being able to modify enough blood stem cells to cure the disease. These cells are rare and live in little niches within the bone marrow, so they are difficult to access with an injection. This approach is still in the research stage of development, but if feasible, an injectable option would make the therapy more accessible to patients without health insurance (or two million dollars).

The other alternative, Orkin says, are pills. "That's the value of knowing how the switch is regulated: if you know what the component parts are, you can target small molecules that work on them, and at least envision a therapy that could be given as a pill." Orkin recognizes that gene therapy is too difficult and expensive to relieve the burden of disease around the world, and pills would vastly improve accessibility. Finding such a drug, although challenging, is something he and his team are actively pursuing.

Whether all these therapies will be successful is still an open question, but one thing is clear: there are many options to investigate, thanks to the blueprint Orkin has drawn. Soon, a diagnosis of sickle cell anemia and related blood disorders may not feel like such crushing news, and new therapies could give more patients a longer, pain-free life.

While attending MIT, Orkin explains, "I thought I was going to become a physicist, but realized very quickly that of the 800 students in the class, 500 would be just as good a physicist as me." He then found a smaller pond in the burgeoning field of molecular genetics.

"It took a while to figure out what the right path was," he says. "Do what interests you. If it doesn't interest you, no amount of coaxing is going to get you very far. Science can be quite frustrating." Orkin persevered, and is now a recipient of the 2022 Canada Gairdner International Award.

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.

Zulfiqar Bhutta:

Read: R. Thygesen and A. Mortazavi. "**Healthy Mothers and Children Make for a Healthy World**" (article, comic and/or video). *Canada Gairdner Awards 2022 Laureates Education Materials,* pp2 - 5

Learning Objectives:

1. Become familiar with examples of social determinants of health that may affect the health of individuals in marginalized or poorly resourced communities.

2. Explore how socio-economic status, in particular, relate to social determinants of health.

3. Consider how many of these determinants are quite complex and nuanced, and dependent on a variety of factors beyond just being poor.

Supplementary Reading:

Dr. Bhutta is a huge advocate of improving global health, especially in developing countries where medical infrastructure may be poor or lacking. And as noted in the reading, when viewed from the development lens, the **social determinants of health** play a key role in the disparity of health measures in rich versus poor locales.

One of the most obvious inequities is simply the ability to access life-saving medicines. This problem is further amplified by costs associated with certain health measures (i.e. the cost of a therapeutic drug or the cost of owning and operating a piece of equipment), which often leads to a devastating effect where someone will live or die based only on how rich or poor they are.

This **access to medicine** scenario is also especially keen when it comes to pharmaceutical drugs. Here a lifesaving medicine might have **patents** that keep price tags competitive in rich markets (almost always at a huge profit margin), but exclusionary in poor markets. Note that when the patents run out, the pharmaceutical company will lose control of who can make and set prices for the drug. When this happens, then **generic** versions of the same drug can appear at much lower cost.

Pharmaceutical companies tend to be aggressively protective of their patents because the pipeline to developing effective new medicines is very expensive, and the patents allow them to protect their investment. In other words, without those protections, the argument is that the innovation and business incentive to create new medicines may be stifled. That being said, it could also be argued that the presence of these same patents, that prohibit any generic options, is a literal death sentence to those in poorer countries.

Classroom Activity: Patents on Life Saving Medicines: The Debate.

Supplies: None.

Time: Homework: minimum of one hour, but more is also encouraged.

Time need to conduct the debate. There are a variety of different formats that the teacher can use. A google search will give you many options if you're not familiar.

Description: The classroom will be split into two teams for a debate on the access to medicine issue. The two stances will be as follows: each team can be assigned the stance by the teacher.

(1) AFFIRMATIVE STANCE: That pharmaceutical companies should be entitled to their patents, and therefore restrict the production of generic (cheaper) versions of their drugs.

(2) OPPOSING STANCE: That access to medicine should be a human right, and therefore there should means to allow access to cheaper versions of the drugs for patients in poorer locales.

For the teacher: You can provide a few hints to the teams on how to go about this. This can include looking up:

(i) The drug development pipeline (the stages and the potential costs associated with the development of the new drug).

(ii) What a generic is and how they work.

(iii) Looking up "access to medicine" but with HIV drugs in particular. HIV was an interesting scenario because with drugs, it is effectively a chronic but easily manageable disease, whereas without drugs, it leads to death. There were a number of past high profile patent cases around access to these drugs in particular.

(iv) The notion of a compulsory license.

(v) Students can also look up efforts around access to COVID-19 vaccines. Note that even though there are programs to address the access issue (i.e. COVAX or the "COVID-19 Vaccine Global Access Facility"), it's also clear that there are still inequities at play, such as the speed and volume of access and which type of vaccine is available.

Purpose: This exercise very much allows students to see how social determinants of health have huge impacts, but also that they can be very nuanced sometimes.

Discussion Questions:

1. Just one discussion question: given the two stances presented in this exercise, where do you personally fall? Can you explain why? And can you also see the other side, or do you think this should be an easy choice?

Activity designed by David Ng

Deborah J. Cook

Read: B. Hay and A. Mortazavi. "**Transforming Care for the Critically Ill and the Dying**" (article, comic and/or video). *Canada Gairdner Awards 2022 Laureates Education Materials,* pp6 - 10

Learning Objectives:

1. Learn about how intensive care relies on a team of medical professionals.

2. Understand the complex and interdisciplinary nature of the critical care team that oversees a critically ill or dying patient.

Supplementary Reading:

Teacher note: Although this activity is fairly low key, be aware that there may be a chance that it is triggering for students who have recently gone through a process where a loved one has experienced ICU or critical care processes. Therefore, it might be appropriate before the activity, to discretely inform the students that they can email you if they feel they may be uncomfortable around such an activity. This way, you can assess whether you want to do it or not with your class.

Patients who end up in intensive care often have a multitude of issues that need medical intervention. This same challenge is also often seen for those who are critically ill or at end of life. Essentially, in these cases, the health of the individual may be severely compromised due to many issues in many different areas of the body.

Consequently, there tends to be many roles involved in assembling a team for the intensive care unit (ICU), way beyond just having primary physicians and nurses. These patients may need extensive care from trained professionals such as cardiologists, oncologists, surgeons, clinical psychologists, and even spiritual care providers.

Dr. Cook's work, in particular, has been pivotal in gathering evidence that creates best practices in how such teams should be assembled for the benefit and comfort of the patient.

Classroom Activity: Healthcare Team Matching Game

Supplies: Print out two copies of the 3 page sheet that highlights the specific medical role and the tasks that that role tends to oversee (see pages 35, 36, and 37). Each copy will be cut along the dotted lines so that you have a pile of notes that have the role titles and the role tasks. In this way, you will have two separate piles of notes.

Print one extra copy of the sheet, as a teacher reference. Note that there are 21 roles in the printout.

Time: 30 to 45 minutes.

Description: To begin, split the classroom into two teams. Make sure each team has its own pile of notes (from the cut pages that highlighted roles and tasks). Get each student to randomly pick a single note, and do this until all notes are picked up (depending on the size of the class, students will likely have at least 2, but possibly 3 of these notes)

Each team will then work to match each of the critical care team roles with the accurate task description.

Award 20 points for being the first team, but also 5 points per correct match. Calculate which team wins!

Purpose: Dr. Deborah Cook is a clinician and educator that has used her decades of research to improve patient-centered care in intensive care units (ICUs) across the world. Her insight and research is noteworthy because it has transformed the field of critical care research, directly benefiting the care and support given to critically-ill and dying patients. From this exercise, students will have the chance to explore the diverse team of individuals that make up a critical care team.

Discussion Questions:

1. Reviewing the list of roles, comment on what sort of team might be required for a patient with brain cancer, or one who suffers from a heart condition, versus a patient who is very advanced in their age.

2. Comment on which of the roles have additional roles in making sure the patient is comfortable, both from a pain point of view, but also in terms of emotional and psychological support.

3. Concerning their end-of-life care, patients had asked Dr. Cook and her team for simple requests to ease their last moments. What is one simple request that you can think of?

4. In discussions around end of life care, there tends to tension between doing whatever is necessary to extend life, such as an intervention that could be quite traumatic (i.e. surgery): versus letting go, so that the patient can submit to palliative care where they will experience less pain and trauma. Discuss which you feel is the better option, and why.

Activity designed by Sean Vidal Edgerton.

To print and cut along dotted lines

CLINICIAN	**- Works one-on-one with patients.** **- Helps to diagnose & treat illness of the patient. Observes vitals.** **- May have a medical specialty, such as pathologist, physician, registered nurse, clinical psychologist, dietician, surgeon, etc.**
CARDIOLOGIST	**- Physician who specializes in the cardiovascular system (heart and blood vessels).** **- May further specialize as a Critical Care Cardiologist, and is responsible for ventilator management, mechanical circulatory equipment and protocols, neurologic emergencies, etc.**
RADIOLOGIST	**- An expert consultant to the critical care team and physician.** **- Specialize in the diagnosis and treatment of disease or injury by using medical imaging equipment (such as CT scan, MRI, X-ray, ultrasound).** **- Analyze medical images to help diagnosis the disease or injury.**
NEUROLOGIST	**- A clinician who focuses on the diagnosis, treatment, and management of diseases/pathologies affecting the nervous system (brain and pinal cord), peripheral nerves, and muscles.** **- In a Neuro-ICU, may care for patients with immediate life-threatening neurological issues or trauma,**
ONCOLOGIST	**- A clinician who focuses on cancer, such as the treatment of cancer, appropriate medical care, and diagnosis.** **- Alongside the critical care team, addresses any cancer-specific treatments and side-effects that may complicate concurring ailments, treatments, or exascerbate potential complications.**
BEDSIDE NURSE	**- Record and access patient baseline & current functional status.** **- Gather mental status of patient: cognition, social support, living situation, mood, nutritional status.** **- Begin to implement preventative protocols to the patient.**
PHYSICIAN	**- Perform non-surgical duties, such as a preliminary diagnosis, treatment, health status, or problem with the patient.** **- Record the patient's past medical history.** **- Explore treatment plans, length of stay, care, and referrals.**

To print and cut along dotted lines

INTENSIVIST	**- Board-certified Physician who provides special care for critically ill and dying patients. - Admits patient(s) to the ICU alongside the critical care nurse. - Assess patient status, providing advice to critical care team, making quick decisions, with say on final decisions and treatment**
RESPIRATORY THERAPIST	**- Performs respiratory care modalities and cardiopulmonary technology duties for patients who have trouble breathing. - Help to diagnose & treat cardiovascular and pulmonary disease. - May perform cardiopulmonary resuscitation (CPR), external cardiac massage, and artificial respiration.**
PHYSIOTHERAPIST	**- Alongside bedside nurse, assess patient's mobility any limitations or challenges. - Assessment of gait with movement plans and exercises. - Determine if extra or specialized services (rehab, etc.)**
ANESTHESIOLOGIST	**- Manages anesthesia and delivery during surgeries. - Evaluates the status of the patient before, during, and after anesthesia is administered for surgery. - Ensures patient awakens from anesthesia safely and may prescribe pain-relieving medications post-surgery.**
CLINICAL PHARMACIST	**- Alongside the physician, determine which medications are appropriate as well as inappropriate for the patient. - Prepare to record response to medication or have plan to change if using high-risk medications.**
DIETICIAN	**- Determine the baseline nutritional status of the patient. - Record any dietary conditions or ailments and recommend nutritional plan to the patient. - Work with critical care team on speech therapy, oral feeding, etc.**
SPIRITUAL CARE PROVIDER	**- Clinically trained; they may offer the patients, immediate family, and loved ones spiritual and religious guidance across diverse beliefs and cultural traditions. - Assess the role of spirituality in the patient's life and their understanding of disease. Deals with mortality, coping, recovery.**
CLINICAL PSYCHOLOGIST	**- Meet with patient and identify any mental, emotional, or behavioral problems in their lives. Assist the patient as needed. - May observe the patient in various situations to assess and interpret mental health status or disorders. - Talk with the patient to understand what may be affecting them.**

To print and cut along dotted lines

SOCIAL WORKER	**- Order proper and durable medical equipment for the patient.** **- Identify resources that will directly benefit the patient (such as care, finances, living options, etc.)** **- Coordinate ICU discharge and plan with the critical care team.**
LABORATORY TECHNICIAN	**- Familiar with medical equipment, reagents, labortatory protocols, and medical testing.** **- Analyze patient samples, produces results, and forwards these findings to the critical care team to make a formal diagnoses.** **- Ensures lab testing is done thoroughly and accurately.**
CLINICIAN-IN-TRAINING	**- Is a student or resident with degree and currently in medical training to become a Clinician; shadows the Clinician and team.** **- Works under the Clinician to help with appropriate duties.** **- As a trainee, is developing a clinical specialty or subspecialty relating to their advisors (clinicians, etc.)**
ADMINISTRATIVE AND CLERICAL STAFF	**- Identifies and relays any patient concerns to Physician and staff.** **- Collects and gathers all of the patient's information and medical records from the critical care team.** **- Organizing and filing proper documents of the patient; data entry, answering phone calls and emails, schedules appointments.**
CLINICAL RESEARCHER	**- Conducts, designs, and performs clinical trials. The patient is usually recruited and screened by the Clinical Researcher.** **- Briefs the critical care team on how to conduct trials.** **- Maintain ethical practice, stays strict to norms and regulations, as well as submitting tests and formal reports of patient.**
REGISTERED NURSE	**- Works alongside the physician and the critical care team to observe, record, and monitor patient status and symptoms.** **- Stay consistent and vigilant with the patient concerning reactions, status, or progress/** **- Administer medications to patients and monitor side effects.**

Pieter Cullis:

Read: B. Black and A. Mortazavi. "**Lipids, Nanoparticles, and Beyond**" (article, comic and/or video). *Canada Gairdner Awards 2022 Laureates Education Materials,* pp11 - 15

Learning Objectives:

1. To learn about the basic chemical properties that lipids have.

2. To explore how these structures might self-assemble in aqueous (water based) solutions.

3. To become familiar with the terms: lipid bilayer, liposome, and micelle.

Supplementary Reading:

The membranes of our cells are primarily composed of lipids known as phosopholipids. This important molecule is responsible for creating the outer physical shell of our cells, and therefore represent a way for the internal elements of cells to be separated and protected from the outside.

Dr. Pieter Cullis' work essentially explored the variation and behaviour of such lipids, which led to insight on how one could design materials that cross the membrane efficiently, and therefore act like a "delivery system." For instance, this might include creating chemistries that could deliver drugs into specific cells, or (as the article highlights) deliver pieces of code that can express proteins that activate a vaccination type immune response.

Key to the lipid structure is the fact that it can be broken down to two key parts: one being **hydrophobic** (water hating), and the other being **hydrophilic** (water loving). In fact, if we were to draw a structure out Pictionary style, it could be nicely represented in the following manner (like a lollipop)!

This part is hydrophilic (LOVES water)

This part is hydrophobic (HATES water)

Since there are different types of lipids, one could also envisioned these doodles where the ball part may be bigger or smaller, or the tail part, likewise being bigger or smaller. As well, these two parts may also have quirks in how they interact (i.e. the ball whilst always hydrophilic may also have other binding preferences).

All in all, this simple structure lends itself to an opportunity to see how such molecules might self-assemble when placed in water. This activity is designed to explore this.

Classroom Activity: Lipid doodles!

Supplies:
Paper and pens/pencils
Access to a whiteboard or blackboard. Alternatively, a slide can be projected.

Time: 30 to 45 minutes.

Description: In this activity, you will ask students to doodle lipid structures (i.e. lollipops) to see how they can form discrete structures.

Setting up: Begin by breaking up the classroom into groups of 4-6 students. Next, scribble on a blackboard/whiteboard (or provide via slide) the illustration seen on page 40. Note how there are four doodling tasks in this picture.

Going over the rules phase: Then tell the groups to draw pictures of how these lipid structures might self-assemble. You can define the rules as

follows:

"The circles (hydrophilic) will always want to be next to the water, whereas the tails would always want to interact only with each other. For structures that have positive or negative signs, you also want to make sure the same signs are not next to each other."

The doodling phase: Each group can then use an area of the paper to work on each of the four tasks (or for the sake of time, you can have different groups assigned to different tasks). For this, you can give them about 5 minutes for each task, or about 20 minutes total.

The debriefing phase: After doodling, you can debrief with the students to share what types of structures they drew, and then take a peek at the discussion questions below.

Purpose: Dr. Pieter Cullis's research is noteworthy because it led to the discovery of lipid nanoparticle (LNP) technology, with hugely impacts on the fields of medicine and molecular biology. By experimenting with a variety of lipid structures, he developed a system of model membranes (i.e., artificial membrane vesicles) that could be ionized (have its charge changed) and manipulated depending on the cellular and physiological environment.

Discussion Questions:

1. Ask the students to look up the following terms: **lipid bilayer**, **liposome**, and **micelle**. Were any of these structures drawn? (note that the liposome structure specifically is the one that Cullis played around with to create a delivery system!)

2. If you were designing a liposome and you needed the liposome to be bigger (to hold a larger drug for instance), what structural features do you think would be needed for the lipids you use (hint: think about how you might want to change the circle and tail components)?

3. Continuing with the Pictionary concept, it turns out that if you got the word "soap," you would also draw something very similar to the lipid (a structure having a hydrophilic and a hydrophobic section). Given this, can you discuss why adding a soap might be great way to break or lyse cell membranes?

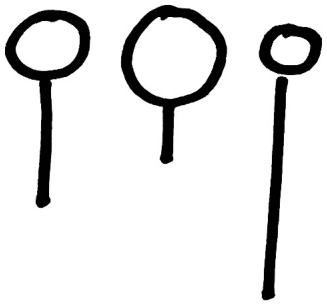
4. *(For older students who have covered the concepts of pI)* In the reading, it was noted that cationic (or positively charged) lipids were actively removed by the immune system, representing a problem with using them for delivery. Moreover, Cullis figured out a way to switch the charge of the lipids, so that it was one charge when en route, and then a different charge going in. If the pH of the cell is different than the outside environment, how might this charge switch happen (hint: think about how pI is important in determining the charge of a molecule).

Activity designed by David Ng and Sean Vidal Edgerton.

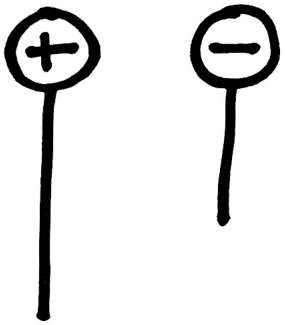
Here are 4 doodle tasks. Note that for the 4th one, the charges are only at the top of the lipid molecule (not the sides)

1.

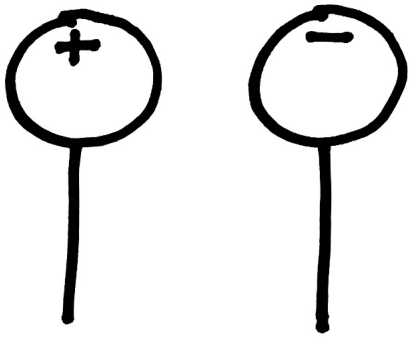
2.



3.



4.



John E. Dick:

Read: H. Gerrie and A. Mortazavi. "**Unlocking the Mystery of Stem Cells**" (article, comic and/or video). *Canada Gairdner Awards 2022 Laureates Education Materials,* pp16 - 20

Learning Objectives:

1. Understand how healthy cells can become cancerous.

2. Explore the different ways that cancer-causing mutations can occur, and the environmental factors that can cause them.

3. Understand that cancer is often the accumulation of cancer-causing mutations;

4. Learn how to reduce your risk of getting cancer.

5. Define "precision medicine" and "precision oncogenomics."

6. Understand how each cancer cell is unique, requiring a personalized approach to treatment.

Supplementary Reading:

What are oncogenes?

Oncogenes are genes that have the potential to cause cancer. They are the mutated forms of "proto-oncogenes," normal cellular genes that act to stimulate cell division or inhibit cell death in healthy cells. Unlike proto-oncogenes, oncogenes can cause unhealthy cells to divide continuously, even when they weren't explicitly instructed to by pro-growth signals. This is how oncogenes can lead to cancer: by allowing tumor cells to grow uncontrollably and eventually spread to other part of the body.

Types of Oncogenes:

Receptor tyrosine kinases: proteins responsible for phosphorylating (adding a phosphate group to) molecules such as growth factors. This activates a downstream molecule, allowing it to exert an effect elsewhere in the cell.

Receptor-associated kinases: when activated, these proteins act to transmit signals to the cell's nucleus, often altering gene expression by increasing or decreasing protein production.

Telomerase: this protein inhibits chromosomes from shortening during replication, preventing the loss of important genetic information over time.

Apoptosis regulating proteins: these proteins manage programmed cell death, known as "apoptosis." They ensure that cells "self-destruct" in the event of harmful mutations or replication errors, preventing cells from becoming cancerous.

Transcription Factors: these proteins bind to the DNA helix and are essential for targeted gene expression.

Membrane associated signal transducing molecules: When activated, these proteins catalyze a cascade of events that ultimately alters cell behaviour. Instead of being activated directly, they are indirectly activated by the binding of nearby receptors.

While cells can sometimes become cancerous from single mutations, more often a cancer cell contains a variety of cancer-causing mutations. These cumulative "hits" over a lifetime can eventually lead to cancer when a cell acquires too many.

What causes mutations?

Chemical or physical agents capable of inducing mutations are known as **mutagens**. Mutagens cause changes in an organisms' genetic information. In some cases, these genetic changes can cause or contribute to certain diseases, like cancer. Some examples of mutagens include: ultraviolet (UV) light, alcohol, pathogens, and certain metals.

While cells can sometimes become cancerous from single mutations, more often a cancer cell

contains a variety of cancer-causing mutations. These cumulative "hits" over a lifetime can eventually lead to cancer when a cell acquires too many, and begins to replicate uncontrollably.

Why do mutations matter in cancer treatment?

Precision medicine is the concept of using a patient's genetics, environment, and lifestyle to identify a disease treatment that can suit them best. Precision medicine can be as simple as blood typing before a blood transfusion, or as complex as using a tumor's genetic profile to inform a patient's cancer treatment, known as **tumor profiling**.

Tumor profiling, pioneered by scientists like Dr. Dick, can provide valuable information to physicians treating cancer patients. Using genetic screening to inform disease treatment helps to connect patients with therapies that are far more likely to be effective than one prescribed using the traditional "one-size-fits-all" approach. This is particularly true in oncology, the study of cancer, as cancer is a highly individual disease. With each patient carrying unique combinations of genetic risk factors, routine tumor profiling for individual patients can be extremely effective in guiding therapy for these individuals: connecting cancer patients with appropriate treatments more quickly.

Classroom Activity: Stem Cell Jenga

Supplies:
- A set of Jenga blocks
- 6-sided die
- Printed "Cancer mutations" list, cut out, and taped/glued to jenga blocks

Time: 20 to 30 minutes, optional additional 15 minute activity.

Description:

Set up: Before class, teachers print, cut out, and tape 54 Jenga-sized strips of paper to individual Jenga pieces (see pages 44 to 47). Each cut-out has a gene name, a description of its function, and the type of cancer it has been implicated in.

During class, teachers assemble a Jenga tower, representing a healthy cell, and have students take turns drawing pieces. Before drawing a piece, students roll a 6-sided dice, match the number to the list below, and read aloud the type of mutation associated with the number. Each time a new type of mutagen is drawn, read its description out loud.

1 - UV exposure: Lower-energy radiation, such as UV rays, can penetrate cellular and nuclear membranes. One way this penetration can damage DNA is by cross-linking (chemically gluing) two bases together, or causing double-stranded DNA breaks. Wearing sunscreen can reduce the harmful effects of UV rays by reflecting them away from your skin.

2 - Alcohol: All alcoholic drinks, including red and white wine, beer, and liquor, are linked with cancer. When you drink alcohol, it is processed by the liver into an organic chemical compound called "acetaldehyde." Acetylaldehyde, while less toxic than alcohol, induces a chemical pathway that is known to produce mutagenic compounds. The more alcohol you drink, the higher your cancer risk.

3 - Age: Age is a well-recognized risk factor for cancer development. The normal aging process affects many important biological processes within our bodies that result in the deterioration of proteins and DNA in cells. Many of these damaged cells enter a state of arrested growth, called "senescence"—no longer dividing and growing, but still remaining metabolically active and capable of causing problems. The longer we live, the more errors our genes accumulate. Over time, if enough of these errors are in proto-oncogenes, these mutations can lead to cancer.

4 - Metal: Many metals and their compounds may be mutagenic. Arsenic, chromium, iron, and nickel may be associated with the production of radical oxygen species (ROS): highly reactive chemicals formed from O2. While ROS are by-products of the normal metabolism of oxygen, overproduction of ROS may result in the production of many base adducts, as well as DNA strand breaks and crosslinks. A diet rich in antioxidants

such as blueberries, spinach, and dark chocolate can protect your cells from ROS.

5 - Pathogens. Pathogens such as viruses and bacteria can affect DNA structure, potentially causing cancerous mutations. One example is the Rous sarcoma virus (RSV), which inserts itself into the genome and disrupts genetic function, causing sarcomas in chickens. Using proper hand hygiene destroys viruses and bacteria on your skin before they can cause harm.

6 - Plastic products. Some of the chemicals in plastic products, such as bisphenol A (BPA), have been suspected of causing cancer in people. BPA is a weak synthetic estrogen found in many rigid plastic products, food and formula can linings, dental sealants, and on the shiny side of paper cashier receipts (to stabilize the ink). Its estrogen-like activity makes it a hormone disruptor, like many other chemicals in plastics. Hormone disruptors can affect how estrogen and other hormones act in the body, by blocking them or mimicking them, which throws off the body's hormonal balance, sometimes causing cancer. While it's likely impossible to completely avoid all plastic products, it's best to use as little plastic as possible, and never use it around food.

After identifying the type of mutagen, students remove a Jenga piece, read it outloud, and list the mutagen type and oncogene name on the whiteboard. This process is repeated until the Jenga tower falls.

When the Jenga tower falls over, explain to the students that the cell's health was sufficiently weakened by oncogenes, and has now become cancerous.

Repeat this activity until 3+ lists of oncogenes are produced, each representing the tumor profile of a now-cancerous cell.

While some of the lists have overlapping oncogenes, each list (should be) unique. This signifies how cancers can vary between people and even between cells as different mutations accumulate.

Purpose: Dr. Dick's research was innovative to cancer research because it challenged the notion that certain types of cancers (breast, colon, etc) should be treated the same. Students will explore actual cancer-causing mutations to help them understand how cancers can vary between people and even between cells as different mutations accumulate. This will help them understand the utility of tumor profiling in determining the precise genes involved in cancer so that physicians can tailor medicine to the unique genetics of individual patients.

Discussion Questions:

1. (from reading) What are stem cells? Why is it more dangerous for a stem cell to become cancerous than a cell with an established fate (e.g. muscle cell or blood cell).

2. (from oncogene list) Review the oncogene blocks you drew and their functions. Define any terminology you are unfamiliar with. How do each of your oncogenes function to cause cancer in healthy cells?

3. (from oncogene lists) A few of these oncogenes cause "translocations." What is a translocation? What is the nomenclature used to describe translocation events?

4. What is precision oncogenomics? How can tumor profiling help doctors treat cancer?

5. What mutagens do you encounter on a day-to-day basis? What actions can you take to reduce your exposure to mutagens and decrease your individual cancer risk?

6. Optional topic for in-class debate: What are the advantages and disadvantages of precision medicine in the context of cancer treatment?

(a) Are the expenses associated with tumor profiling worth the cost?

(b) How might access to personalized oncogenomics differ in countries (like Canada) with universal healthcare vs. in countries without?

Activity designed by Marie Johns

Oncogene	Function/Activation	Cancer*
ABL1	Promotes cell growth through tyrosine kinase activity	Chronic myelogenous leukemia
AKAP13	Guanine nucleotide exchange factor	Myeloid leukemias
ALK	Encodes a receptor tyrosine kinase	Lymphomas
ALK/NPM	Translocation creates fusion protein with nucleophosmin(npm)	Large cell lymphomas
AXL	Encodes a receptor tyrosine kinase	Hematopoietic cancers
BCL-2, 3, 6	Block apoptosis (programmed cell death)	B-cell lymphomas and leukemias
CCND1	Encodes cyclin D1. Involved in cell cycle regulation.	Breast and squamous cell carcinomas
CSF1R	Tyrosine kinase	Sarcoma
DEK/NUP214	New protein created by fusion	Acute myeloid leukemia
ERG/FUS	Fusion protein created by t(16:21) translocation.	Myeloid leukemia
ETS1	Transcription factor	Lymphoma
EWSR1/FLI1	Fusion protein created by t(11:22) translocation.	Ewing Sarcoma
FES	Tyrosine kinase	Sarcoma
FGF3 (INT-2)	Encodes a fibroblast (skin cell) growth factor	Breast and squamous cell carcinomas
FGF4	Encodes fibroblast growth factor.	Breast and squamous cell carcinomas

GLI1	Transcription factor	Glioblastoma
GNAS (GSP)	Membrane associated G protein	Thyroid carcinoma
HER2/neu	Overexpression of signaling kinase due to gene amplification	Breast and cervical carcinomas
IL3	Cell signaling molecule	Acute pre B-cell leukemia
KIT	Tyrosine kinase	Sarcoma
KRAS	G-protein. Signal transduction	Lung, ovarian, and bladder carcinoma
K-SAM	Fibroblast growth factor receptor	Stomach carcinomas
LCK	Tyrosine kinase	T-cell lymphoma
MAS1	Angiotensin receptor	Mammary carcinoma
MCF2 (DBL)	Guanine nucleotide exchange factor	Diffuse B-cell lymphoma
MCF2L (OST)	Guanine nucleotide exchange factor	Osteosarcomas
MDM2	Encodes a protein that inhibits and leads to the degradation of p53	Sarcomas
MLLT11	Fusion protein created by a translocation t(11;19).	Acute leukemias
MLLT11	Transcription factor/methyltransferase	Acute myeloid leukemia
MOS	Serine/threonine kinase	Lung cancer
MYB	Transcription factor	Colon carcinoma and leukemias
MYCL	Transcription factor	Lung carcinomas

MYH11/CBFB	New protein created by fusion of transcription factors via an inversion in chromosome 16.	Acute myeloid leukemia
NFKB2	Transcription factor.	B-cell lymphoma
NRAS	G-protein. Signal transduction	Breast carcinoma
NTRK1	Receptor tyrosine kinase	Colon and thyroid carcinomas
PAX-5	Transcription factor	Lympho-plasmacytoid B-cell lymphoma
PBX1/E2A	Fusion protein formed via t(1:19) translocation. Transcription factor	Acute pre B-cell leukemia
PIM1	Serine/threonine kinase	T-cell lymphoma
RAF1	Serine/threonine kinase	Many cancer types
REL/NRG	Fusion protein formed by deletion in chromosome 2. Transcription factor.	B-cell lymphoma
ROS1	Tyrosine kinase	Sarcoma
RUNX1 (AML1)	Encodes a transcription factor	Acute myeloid leukemia
RUNX1/MTG8(ETO)	New fusion protein created by translocation	Acute leukemias
RUNX1T1	Fusion of transcription repressor to factor to a transcription factor.	Acute leukemias
SET/CAN	Fusion protein formed by rearrangement of chromosome 9. Protein localization	Acute myeloid leukemia
SIS (aka PDGFB)	Growth factor	Glioma, fibrosarcoma
SKI	Transcription factor	Carcinomas
SRC	Tyrosine kinase	Sarcomas

TAL1, TAL2	Transcription factor.	Acute T-cell leukemia
TCF3/PBX 1	New protein created by fusion	Acute pre B-cell leukemia
TIAM1	Guanine nucleotide exchange factor	T-lymphoma
TLX1	Transcription factor	Acute T-cell leukemia
TSC2	GTPase activator	Renal and brain tumors

Katalin Karikó and Drew Weissman:

Read: F. Qaiser and A. Mortazavi. "**mRNA: From Instability to a World Changing Vaccine**" (article, comic and/or video). *Canada Gairdner Awards 2022 Laureates Education Materials,* pp21 - 25

Learning Objectives:

1. Review transcription, translation, and the central dogma of molecular biology.

2. Model transcription and translation as students construct polypeptide chains of LEGOs.

3. Understand the utility of mRNA in relaying messages between organelles.

Supplementary Reading:

DNA, short for "deoxyribonucleic acid'', is the genetic material of all organisms on Earth. Most organism's traits, including those of humans, are inherited from a parent through transmission of DNA. This trait information is coded into sequences of nucleotides (As, Ts, Cs, and Gs) in a consolidated form so that it can be easily unfolded and duplicated as cells replicate and divide. Rather than being just a long, boring string of nucleotides, DNA is divided up into functional units called genes. Each gene serves a specific function in the human body, coding for a specific protein product that can act in a number of ways, all of which will ultimately perform a specific job in the cell. For example, the Apolipoprotein E (APOE) gene codes for a protein involved in the metabolism of fats in the body of mammals.

The functional products of most known genes are proteins, or, more accurately, **polypeptides**. With "poly" meaning multiple, and "peptide," meaning proteins, polypeptides are essentially just chains of amino acids. While some proteins are made up of a single polypeptide, many proteins are made up of multiple polypeptides that fold together into complex 3D structures.

During expression of a protein-coding gene, information flows from DNA -> RNA -> protein. This directional flow of information is known as the **central dogma of molecular biology**. There are two major steps to the process of synthesizing polypeptides from DNA, they are known as **transcription** and **translation**.

- Transcription is the process of coping a gene into an RNA molecule so that it can travel outside the nucleus and exert its function. This step is called transcription because it involves rewriting, or transcribing, the DNA sequence in a similar RNA "alphabet."

- Translation follows transcription for most eukaryotic genes. During translation, the sequence of the mRNA is decoded to specify the amino acid sequence of a polypeptide. The name translation reflects that the nucleotide sequence of the mRNA sequence must be translated into the completely different "language" of amino acids. During translation, the nucleotides of the mRNA are read in groups of three called codons. Each codon specifies a particular amino acid or a stop signal.

Classroom Activity: Central Dogma LEGO Relay Race

Supplies:

For each group:
- Data Sheet with the gene sequence to build, as well as the key to translate RNA to lego blocks (see page 50 for printable).:
- A pack of sticky notes
- A few pens

On a shared table in the middle (part of the "cytoplasm") where blocks represent amino acids:
- 30 Green Lego Blocks
- 40 Yellow Lego Blocks
- 65 Red Lego Blocks
- 45 Blue Lego Blocks
- 40 White Lego Blocks
- 20 Black Lego Blocks

Posted at the front of the class (the "nucleus"):
The DNA codes for each gene sheet (see page 51 for printable).

Time: 20-30 minutes

Description:

Set up: Before class, arrange 3 stations:

- The nucleus: area in front of classroom with DNA molecule taped to wall

- The cytoplasm: table in the middle of classroom with all the lego blocks

- The cytoplasm: table at the back of the classroom where blocks will be built.

Put students into teams of around 6. Try to make the teams as evenly numbered as possible

Once students have their teams, ask two persons from each team to volunteer for leading one of the following roles until all roles have at least two students. Extra players can float between all three roles as the need arises during the race:

- The mRNA (messengers): will copy the genes from the front of the class (nucleus) onto a sticky note

- tRNA (transfer RNAs): will get the blocks from the table (cytoplasm)

- rRNA (ribosomes): will build the Lego tower (polypeptide chain / protein) using the lego blocks (amino acids).

Debriefing the team: Read the following:

"In this game, lego pieces will represent amino acids coded by DNA sequences. Your task is to build a lego structure as fast as you can, that is based on the code presented at the nucleus. Here, you will note the three areas of the room. mRNAs will hang out in front of the room (the nucleus), tRNAs will hang out in the middle of the room where the table of lego blocks are (cytoplasm), and rRNAs will be at the back ready to assemble the lego pieces (also cytoplasm).

When I (the teacher) say "GO!", mRNAs will turn over the data sheet and they can copy the recipe for their lego chain one gene at a time on a sticky note. This should complement the DNA sequence data sheet. i.e. AGT -> UCA etc. When a code for first gene is on a sticky note, mRNAs may pass this sticky note to the tRNAs (with the data sheet), who will then deliver the lego blocks ONE AT A TIME to the rRNAs at the back of the room. The rRNAs will then assemble the lego blocks according to the gene code, and when finished will deliver the data sheet back to the mRNAs who will then begin the process all over again with the next gene."

First team to make the correct lego polypeptide chain is the "winner."

Purpose: The purpose of this activity is to help students understand the central dogma of molecular biology. By translating DNA into polypeptide chains, students can conceptualize the utility of mRNA as a genetic "messenger," and better understand Dr. Karikó and Dr. Weissman's mRNA research.

Discussion Questions:

1. Where is the DNA stored in eukaryotic cells? What RNA molecule is used to transfer it out of there? What is this process called?

2. What are the DNA-RNA base-pairing rules?

3. What is the name of the 3 nucleotide segments of mRNA?

4. Which organelle is responsible for making proteins?

5. What is translation and where does it occur?

6. During translation, what pairs up with the mRNA codons?

7. What do tRNA's carry to the ribosome, and what do they form as they link up to form a chain?

Activity designed by Marie Johns, adapted from "Lego Protein Synthesis" worksheet: https://ca01001129.schoolwires.net/cms/lib/CA01001129/Centricity/Domain/1288/Activity%20Lego_Protein_Synthesis.pdf

Data Sheet

Lego Polypeptide Recipe (build 5 "genes" in a row in the following order):

Gene 5, Gene 3, Gene 1, Gene 4, Gene 2

Lego "Genetic Code":

RNA	**Block**
UGG	Blue
CGC	Yellow
UUA	Red
CUA	White
UGC	Black
CAA	Green

DNA codes for each gene:

(This can be left in the "nucleus" area with sticky notes and pencils)

GENE 1: ACGGCGAAT

GENE 2: ACCGCGACC

GENE 3: GTTGCGAAT

GENE 4: AATGATACC

GENE 5: GTTGATAAT

Stuart H. Orkin:

Read: A. McAfee and A. Mortazavi. "**Sickle Cells and a Tale of Two Hemoglobins**" (article, comic and/or video). *Canada Gairdner Awards 2022 Laureates Education Materials,* pp26 - 30

Learning Objectives:

1. Learn about the history and pathogenesis of malaria.

2. Explore the evolution of sickle cell disease and similar evolutionary adaptations to malaria.

3. Conceptualize evolutionary trade-offs: where an increase in the performance of one trait causes a decrease in the performance of another.

Supplementary Reading:

What is malaria?

Malaria is a deadly infection of the red blood cells caused by a parasite called Plasmodium. Plasmodium parasites live inside certain species of mosquitos that can be found in tropical and subtropical regions around Africa and South Asia. Although these parasites do not affect the mosquitos that carry them, they can greatly harm to people, allowing them to spread easily in human populations. Although anti-malarial drugs can treat the disease, it still remains endemic in many countries and regions.

Most human populations with a long history of endemic malaria have evolved a variety of genetic adaptations to malaria parasites because of the strong selective pressure. Some affect red blood cell shape, while others impact enzymes having to do with red blood cell glucose metabolism, and others affect receptors on the surface of red blood cells. Sickle cell disease is an example of a condition caused by evolutionary adaptation to malaria.

Unfortunately the hemoglobins and other red blood cell abnormalities that protect against malaria generally produce anemia or other genetic diseases in a portion of the population, causing significant morbidity and sometimes even death. Where malaria remains endemic, resistance to malaria generally improves fitness enough to outweigh the reduced fitness due to abnormal red blood cells or hemoglobin.

Classroom Activity: In-class debate: Malaria adaptation and disease

Supplies: None

Time:
Day 1: 0- 15 minutes
Homework: 30 to 60 minutes
Day 2: 45 to 60 minutes

Description: After reviewing the supplementary reading as a class (or assigning it as take-home reading), instruct the students to write on the pros and cons of malaria adaptation and sickle cell disease as a homework assignment. This will require them to come up with arguments and brainstorm counter arguments on both sides: On one side, students can argue about the benefits of evading malaria and can share statistics on how deadly it is, helping them to understand why it exists. On the other side, students can discuss what medical problems are caused by sickle cell and related diseases in the present day.

Next day, assign the students to two different groups: Pro-malaria adaptation vs. Anti-malaria adaptation. Give each group 10-15 minutes to prepare bullet points with their main arguments and organize their thoughts. Each student will have 2 minutes to make their arguments. At the end, students will have an opportunity to respond to counter-arguments raised by the opposing team.

At the end of the "debate". Announce the "winning" team, or note that the only winners are scientists like Dr. Orkin who is working to alleviate disease burden for patients around the world that suffer from sickle-cell disease.

Purpose: To teach students about evolutionary adaptation, sickle cell anemia and related malaria-adaptive disorders while helping them to understand Dr. Orkin's life-changing research.

Discussion Questions:

1. What "knowledge gap" was filled by Dr. Orkin's work? What issue did he identify, and how did he "solve" it?

2. What was one thing you learned from the in-class debate? What surprised you, and what didn't?

3. Aside from Sickle Cell Disease, what other malaria adaptations exist in humans? How does each of them protect against malaria, and what health detriments are they associated with?

4. If malaria adaptations like Sickle Cell Disease are so harmful to patients, why are they still so widespread among certain human populations? What is an "evolutionary trade-off" and how does that term apply to Sickle Cell Disease?

5. Malaria adaptations disproportionally affect people with ancestors who were raised in tropical climates, which predominantly include people of African and South Asian descent. How can racial inequality perpetuate health complications for these communities, particularly in countries without universal healthcare?

Activity designed by Marie Johns