gairdner
LES PRIX CANADA GAIRDNER AWARDS

Canada Gairdner Awards 2020 Laureates Education Materials

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

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

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

For more information about the UBC Michael Smith Laboratories, please visit https://www.msl.ubc.ca/

Mammary Gland Mysteries, Solved

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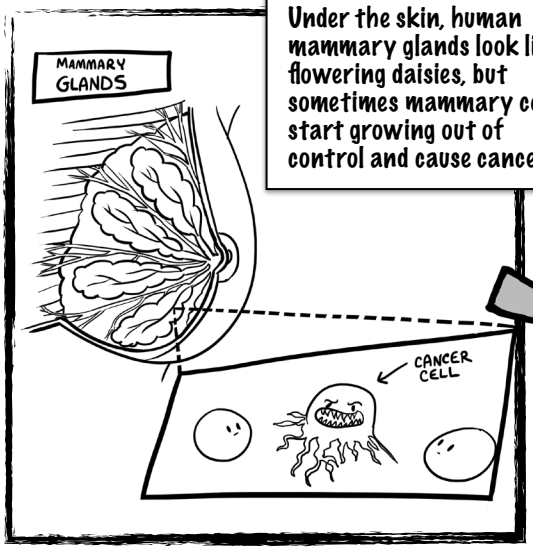

Under the skin, human mammary glands look like flowering daisies, but sometimes mammary cells start growing out of control and cause cancer.

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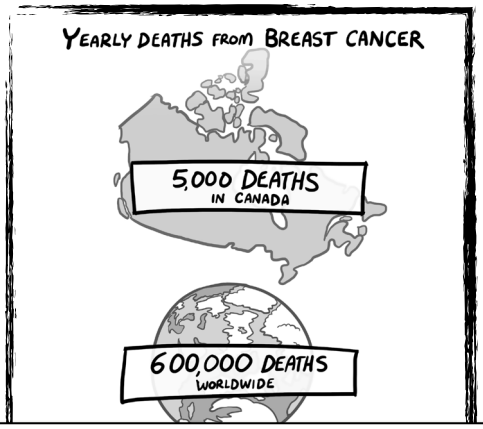

Around 5,000 Canadians and 600,000 people worldwide (mostly women) die from breast cancer each year, and there is still a lot that we don't understand about the disease

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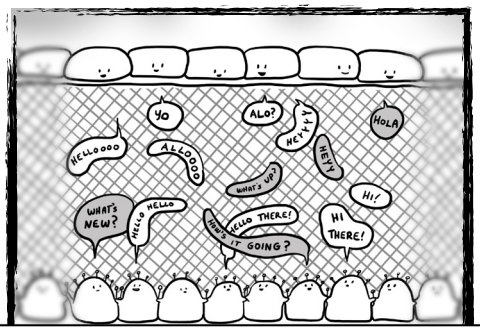

Scientists used to think that the extracellular matrix, the scaffolding surrounding the cells in our tissues, was purely structural. But Dr. Mina Bissell discovered that mammary cells actually communicate with this matrix, and that breast cancer can develop when this communication goes awry – a radical idea, at the time.

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By suspending mammary cells in an artificial matrix, Bissell made the cells behave more like they would in our tissues. Similar methods are now used to culture 'organoids,' or miniature versions of parts of our organs and tissues.

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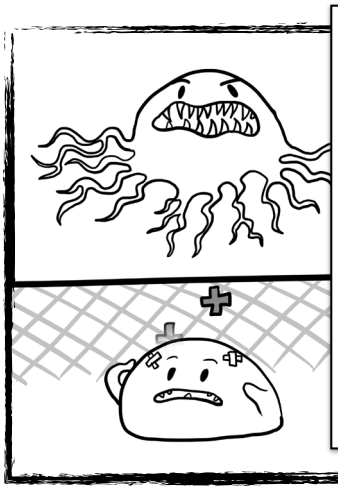

Amazingly, Bissell found that even cancer cells could become healthy again when she restored normal communication between them and their extracellular matrix.

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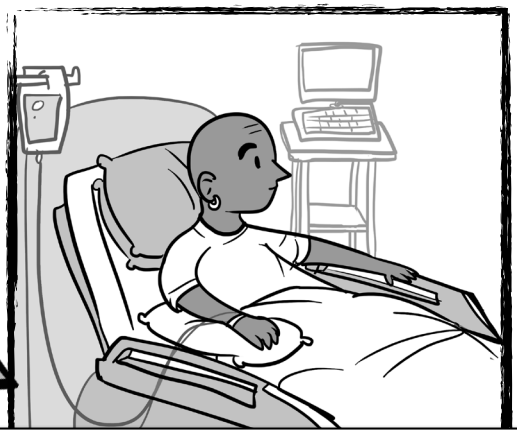


This research has led to a new anti-cancer therapy, which is currently entering clinical trials. All because she wasn't afraid to follow a radical idea.

Art by Armin Mortazavi and text by Alison McAfee. October 2020

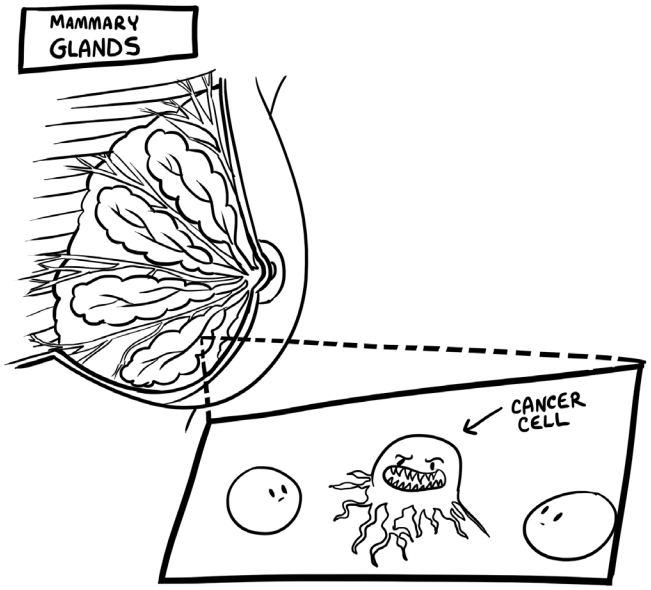
Mammary Gland Mysteries, Solved

The way cells behave depends on more than just their genes, it also depends on what else they can sense around them.

Written by Alison McAfee
Art by Armin Mortazavi

October 2020

Breasts are beautiful organs. No, not in the sexualized sense, but because underneath the skin, **mammary** ducts and lobes form a stunning, radially branching array. Human mammary glands look strikingly similar to daisies, where each of the many lobes is a petal, all attached to the central nipple by ducts that can channel milk for nursing. Sometimes, though, this spectacular architecture goes awry.



In Canada, approximately 27,000 women and 200 men are diagnosed with breast cancer in 2019, with transgender people experiencing intermediate risk. When breast cancer forms, cells in a mammary duct or lobule (raspberry-shaped bundles of cells that make up the lobes) begin growing too fast, marring the exquisite, daisy-like architecture and forming a lumpy tumor instead. Tragically, over 5,000 Canadians and 600,000 people worldwide die from this disease annually, and rates are on the rise.

Dr. Mina Bissell, a professor of biological and systems engineering at the University of California Berkeley, spent much of her career studying breast cancer, including how and why these tumors form. In the 1980s, she discovered that the **extracellular matrix**, the structural scaffolding that surrounds cells in tissues, has a profound influence on how cells behave, including whether mammary cells become cancerous.

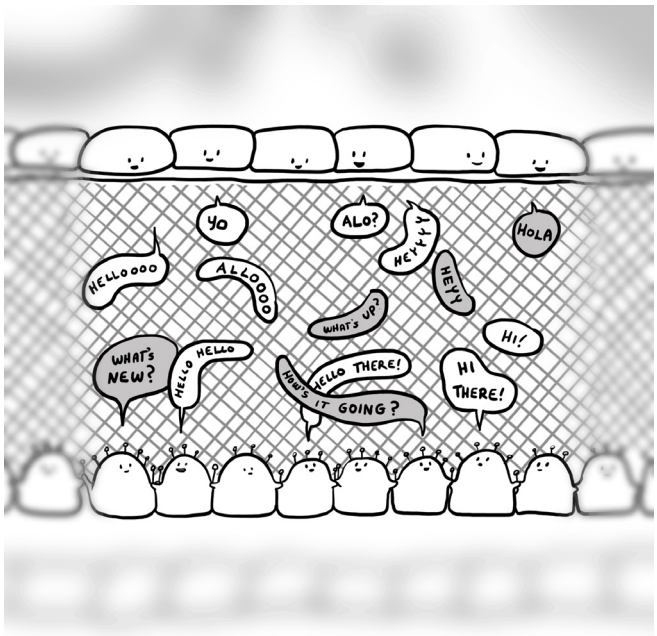
"Originally, I wanted to study glucose metabolism," says Bissell, "but I had a fellowship from the American Cancer Society, and wanted to move to California." Although Bissell did not have her sights set on a career studying breast cancer, she quickly adapted to this competitive field. In the 1970s, she focused her research on the mammary gland, but her discoveries apply to almost all the cells in our bodies.

At the time, there was a long standing belief that a *single* **oncogene** – a mutated gene that can lead to

Extracellular Matrix: *A molecular cobweb connecting cells within tissues. It is primarily made up of large, protein fibers (like collagen and fibrinogen) as well as long chains of sugars (forming a type of molecule called polysaccharides, meaning 'many sugars'). Once thought to function purely as a structural support for cells, we now know it is extraordinarily complex, controlling cell growth, communication, movement, and differentiation.*

rapid cell growth – in a *single* cell was sufficient to cause cancer. However, Bissell wasn't convinced – she reasoned that because we have so many cells in our bodies, between 10 and 70 trillion, that if the belief were true, we should have far more cancer than we do. "This did not make sense to me," Bissell says in her 2012 TED Global talk. Doing the math, "you would be a lump of cancer – you would have cancer all over you – and you're not. Why not?"

She had a hunch that it had something to do with the extracellular matrix, but at first, her colleagues didn't take her seriously. At the time, people thought that components of the matrix were like bricks, and her peers thought she was crazy for suggesting that they could have more complex functions, like being linked to cancer cell growth.



She wasn't dissuaded by the skepticism. After all, an idea wouldn't be radical if it wasn't met with some resistance. Initially, her curiosity piqued when she noticed that cells from mammary glands never grew quite right in the laboratory, and started wondering why. "If you took cells from your skin, mammary glands, tendon, or bone and you put them in culture," says Bissell, "they basically forgot where they came from."

In a flat petri dish, the mammary cells didn't form their normal raspberry-shaped lobules like they do in real tissue, and they didn't secrete milk, which should be their hallmark job. Bissell set out to establish a better culturing system for her experiments, and uncovered something big.

While experimenting with growing the cells in different ways, she found that if she cultured them in a substance that we now call **Matrigel** – a protein jelly that gives the cells an artificial scaffold, letting them grow in 3D space instead of on a flat surface – the mammary cells did something new. They started growing in bundles that looked more like raspberries. They even began secreting milk and producing their own scaffolding proteins around the cell bundles, just like they do in real tissue.

The mammary cells were receiving some kind of signal just by being suspended in a protein jelly, which mimics the context they would normally have in our bodies. This was the clearest demonstration yet that the way cells behave can be dramatically altered by the context, or **microenvironment**, in which they grow.

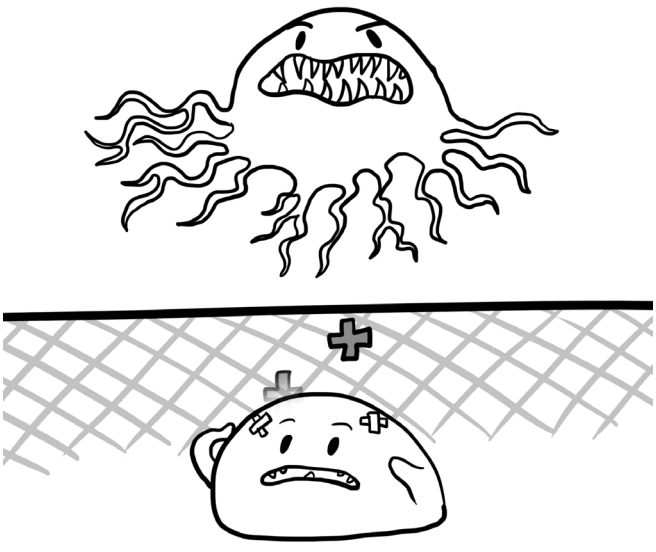
And as Bissell points out, context is everything. "I could see that the culture environment changed the way the cells behaved," she says. "I used to talk about this in the late 70s and early 80s, but people just couldn't appreciate it. I think I was one of very few people who understood that this was intrinsically important."

The cancerous cells also grew in the 3D gel. But instead of looking like raspberries, they looked more like overly mature heads of cauliflower.

Bissell grew up in Iran and, at just 17 years old, she moved to the United States on her own to go to Bryn Mawr – a distinguished women's college (the Ivy League schools did not accept women at the time). During her first year in the bacterial genetics PhD program at Harvard Medical School, she became pregnant with her first child. While her advisor assumed she would drop out, giving up on her education never crossed her mind. After finishing her PhD, she switched disciplines to cancer research, had a second child, and went on to make ground-breaking discoveries. Today, she has won some of the most prestigious awards in science, including the 2020 Gairdner International Award, recognizing her outstanding contributions to cancer research and cell biology.

For some reason, they were not able to properly organize. Cancer cells have so many things wrong with them, it was hard to know exactly why they formed this ugly, disorganized shape. But Bissell had an idea of what it could be.

Scientists have known since the 1960s that cells can communicate with each other using chemical messages, and that this communication goes haywire in cancerous cells. What if cells also communicate with the extracellular matrix, the connective scaffold, that holds our tissues together? Given the results of her Matrigel experiment, it sure looked like they might. Maybe the cancerous cells were not communicating with the logical chatter of normal cells – perhaps instead, they were babbling nonsense.



What if the cancer cells could be calmed down by muting some of this babble between them and their matrix? That's exactly what Bissell tested: She cut off the cells' line of communication by blocking specific receptors on the surface of the tumor cells, which normally allow them to receive signals from the extracellular matrix. Within days, the tumor cells reorganized, transforming into plump little raspberry bundles once again. The cancer was reverted. "It was absolutely incredible," Bissell recalls.

Bissell and her colleagues started their experiments over thirty years ago. Now, their research has led to the development of a new breast cancer therapy, which is currently entering clinical trials. Using this same principle of blocking the tumor cells' receptors (with what are called **inhibitory antibodies**), they hope they can shrink tumors in actual patients, with reduced toxicity compared to conventional treatments. But the impact of this work extends far beyond breast cancer.

The lobules of cells that Bissell grew in Matrigel were some of the first modern examples of what researchers now refer to as **organoids** – artificially cultured cell masses that resemble components of organs. Figuring out how to grow mammary cells in 3D space facilitated a whole new field of organoid research, turning cultured cells into more realistic tissues.

Today, scientists can do far more than grow mammary lobules. They can culture heart organoids that really beat, miniature brains with firing neurons, skin organoids complete with hairs, and many others that resemble simplified versions of the pancreas, lung, liver, and more.

Growing these tiny organoids in the laboratory allows researchers to conduct advanced drug testing before moving to clinical trials, saving time, money, and risk to patients. They make it possible to study infectious diseases, like Zika, meningitis, or COVID-19, in a more realistic context. Organoids can even be grown from a patient's own cells, allowing doctors to test if people with rare conditions will respond to a new drug, or if a chemotherapy-resistant tumor will respond to other treatments.

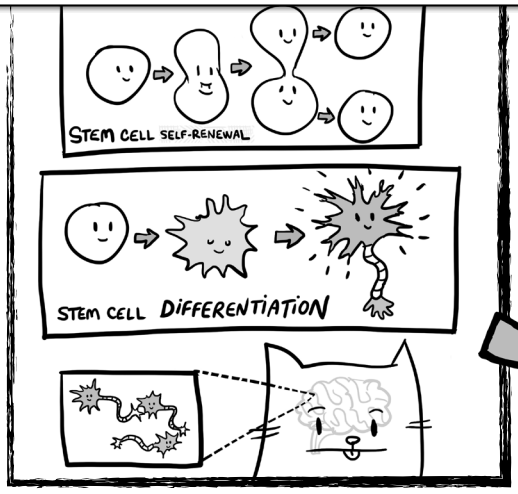
Organoids are not only useful for drug testing – they can also help rebuild parts of your body. One

of the motivations for developing heart organoids was to be able to make laboratory-grown surgical replacements – patches of heart muscle, for example – to repair weak, damaged, or defective tissue. One day, researchers hope to be able to be able to grow larger structures, possibly even whole hearts, for implantation. And it all began with wondering why mammary cells "forgot where they came from" when they were put in a dish.

Science depends on this kind of basic curiosity. Without it, Bissell may never have questioned the entrenched belief that one cell's mutation was enough to cause cancer. She followed her hunch that there was more to the story – that the way cells communicate with their 3D environments was important too – and her discoveries have unapologetically shifted our understanding of multicellular life. "Don't be arrogant," Bissell reminds us, reflecting on the skepticism she received early in her career. "Arrogance kills curiosity."

The Elixir of Life and Our Skin

1 In our bodies, we have a type of cells called stem cells that are special because: 1) they can self-renew (make more stem cells) and 2) they can change into other different types of cells. Only stem cells have these abilities. This is key for living creatures to grow from single cells.



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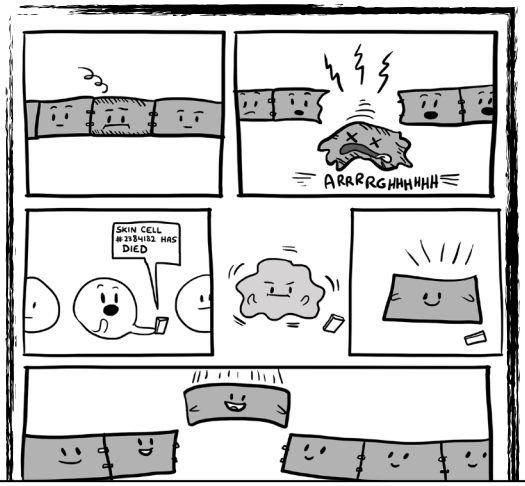
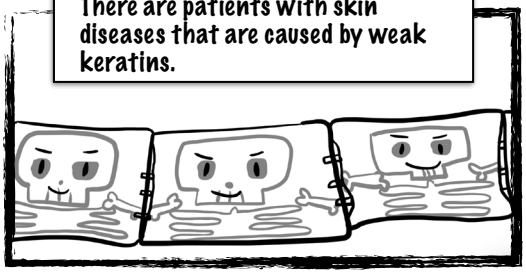


There are stem cells within our skin which help replace dying cells and repair wounds. They divide and then become all the different types of skin cells needed to form our skin.

3 Our skin is resistant to outside forces thanks to a network built by these chain-like structures (kind of like a skeleton) called keratins. There are patients with skin diseases that are caused by weak keratins.



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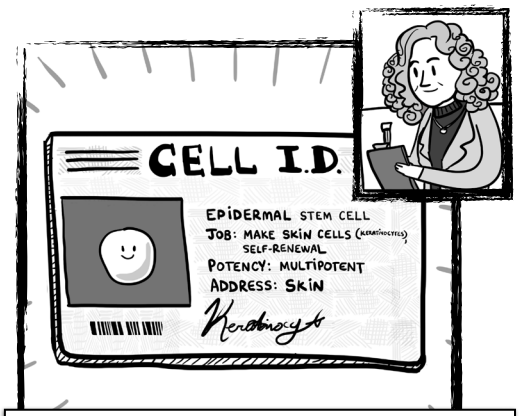

Professor Elaine Fuchs has investigated skin diseases -and other diseases- by trying to learn everything about stem cells.

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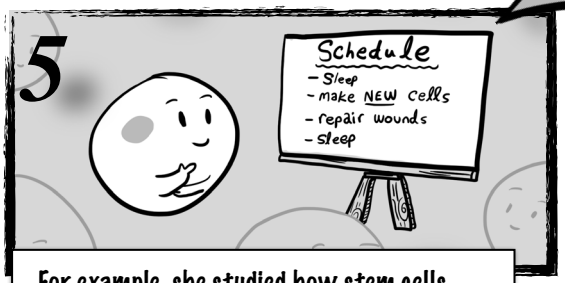
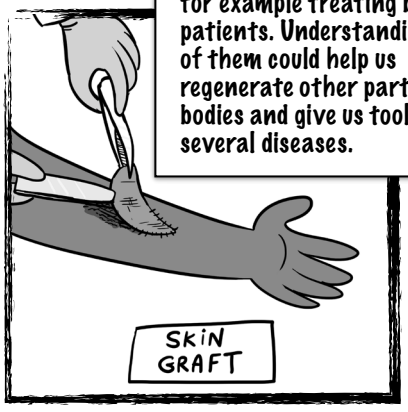


For example, she studied how stem cells experience cycles of rest and action: sometimes they sleep, sometimes they work to make new cells. One time they become active is when they repair wounds.

6 Stem cells have helped us regenerate parts of our bodies, for example treating burn patients. Understanding more of them could help us regenerate other parts of our bodies and give us tools to fight several diseases.



Art by Armin Mortazavi and text by Daniela Salas Acosta. October 2020

The Elixir of Life and Our Skin

Studying the cells of our skin, paved the way for science that explores the possibility of regeneration in medicine.

Written by Daniela Salas Acosta
Art by Armin Mortazavi

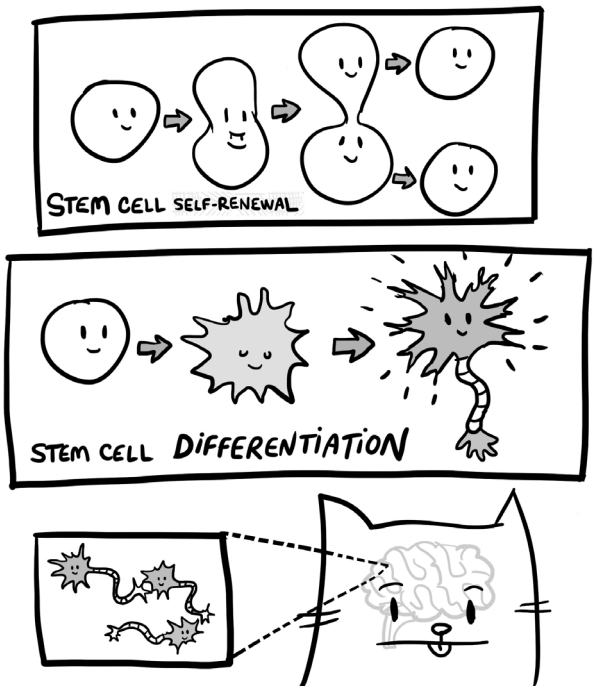
October 2020

Real life examples of fairy tales are everywhere if you look through the right glasses – or in this case, through laboratory lenses. For example, there is actually an elixir of life of sorts, which is even able to regenerate parts of our bodies. And for those who were looking, this incredible possibility was found within our own cells.

What we are really talking about are **stem cells**. These are very special because they have two main abilities. One, they have **potency** – this is the ability to develop, or **differentiate** (kind of like growing up) – into many different kinds of cell types with different kinds of functions. It's as if these cells have enormous potential to become many different things - they haven't committed to any one path yet. Secondly, stem cells can also **self renew** – that is, they have the ability to continually divide into more stem cells which are able to retain their special potency status.

If you think about it, because of these two powerful features, a lot of fundamental biology can happen with stem cells. And here, they play a crucial role in how a *single* cell can grow into mixtures of different cell types, and are able to develop into complex structures such as organs or even an entire organism.

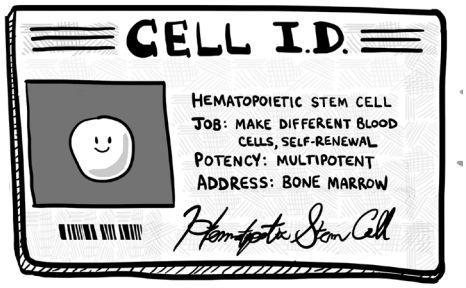
Note that this is very different to the overwhelming majority of cells in your body. Most cells in your body have already differentiated, and have therefore already become specialized. This status means that they have lost potency, in that they are committed to being only that one type of cell. This also tends to mean that your differentiated cells have limited regenerative abilities. This is why stem cells are so special.



This is also where the work of Dr. Elaine Fuchs, a professor at Rockefeller University in New York and one of the 2020 Canadian Gairdner Award winners, comes in. She has dedicated her entire career to studying stem cells, and in particular, the adult stem cells in our skin (or epidermis).

Fuchs was originally a chemist and had never taken a biology or genetics course, but she found herself wanting to work on research related to medicine. She says, "In physical chemistry, you

*Sidebar: There are different types of stem cells according to their potency. A stem cell is more potent if it can differentiate into more cell types. The most potent of all stem cells are called **totipotent** because they can make all the cells required to form a complete organism and also cells that can become placental cells. **Pluripotent** cells can make all the cells of an organism, but they cannot make those needed to form placentas. Sometimes, totipotent and pluripotent cells are referred to as **embryonic cells**, because they tend to only exist in the most early stages of an organism's life.*



***Multipotent** cells is a term for a more restrictive type of stem cell that can also produce many cells, but where they tend to belong to a family with closely related function. However, these aren't limited to early stages of life, and can be found in different parts of the body at any stage of our lives. An example of multipotency are the **hematopoietic stem cells** in our bone marrow, which produce all of our different blood cells. Multipotent stem cells are also often **adult stem cells**.*

can feel that you've answered a question, or you can solve an equation, but in biology, there are so many questions to solve that you can only approximate. And with those approximations, come more questions. It took me a while to recognize that this was what I really loved about biology."

During that transition from chemistry to biology, she attended a research presentation by Prof. Howard Green. He was visiting from MIT to give a seminar about a special type of skin cell. Dr. Green had taken pieces of human skin and had put this tissue in a culture dish. Under the right conditions, he found that he could propagate the cells endlessly, making more and more tissue. These sheets of skin were used to successfully treat patients with terrible burn wounds.

These skin cells could differentiate to make the many different cells found in skin tissue and they could also self-renew. Initially, these skin cells were not known as stem cells but were called **human epidermal keratinocytes**. Today, these keratinocytes would be considered **multipotent adult stem cells** (see sidebar above). Fuchs vividly remembers: "I listened to that talk and I was just enthralled, and I decided soon after that [Dr. Green] was the person I really wanted to work with."

One of Dr. Green's discoveries was that these skin stem cells needed the presence of other cells to grow properly. And so his lab developed techniques where stem cells would be grown layered on top of regular cells. After Fuchs learned how to do this, she used these techniques to become familiar with skin cells and focused her attention on a class of proteins known as **keratins**. Keratins are important because they give our skin the strength to withstand the stress it endures from the environment. "If you rub your skin, you wouldn't expect to see your skin cells ruined after that", says Fuchs, "but if you do the same to your liver, you'll probably ruin your liver".

Her work discovered that these keratin proteins organize in pairs, which in turn further organize in larger numbers to build networks. Furthermore, by understanding the DNA code of keratin, she could do experiments that introduced errors (called mutations) into the keratin proteins. With this, she attempted to examine how those organized networks could become disrupted. And whilst looking at

these disrupted cells, she started to wonder if these types of genetic errors could result in certain human diseases. Fuchs remembers thinking: "There must be patients that have defects in their keratins, but we didn't know where or how to look".

To help pinpoint the genetic causes of disease, Fuchs pioneered a strategy called **reverse genetics**. Basically, this term describes the process of observing the outcomes and symptoms of targeted mutations and *then* attempting to connect those observations with the diagnosis of a disease. It works backwards, or the reverse, of the then common way of figuring out the genetics of a disease. Before reverse genetics, scientists would start with the diseased patients and use their samples to hunt for the mutations responsible. This was not very efficient because they would generally have to compare many genes from many diseased and healthy patients, all with the hope of finding interesting genetic differences.

With her reverse genetics strategy, Fuchs introduced the keratin mutations into a mouse and observed the effects on the animal. In this case, the mouse would be seen to form blisters coming from the layer of mutated stem cells in the skin. She then worked to correlate those symptoms with existing skin diseases. Because she didn't have a medical degree, Fuchs and her team searched the medical literature. "We bought a dermatology textbook," she recalls, "and compared the symptoms point by point, and found a disorder called epidermolysis bullosa simplex that would cause blistering just from washing your face." The similarities were so striking that she knew that this disease was related to those keratins.

Fuchs' work on keratins was a breakthrough on its own right but her subsequent contributions were equally important and were more focused on the very fundamentals of stem cell biology. In particular, she was inspired by observations noted from the burn patients who were treated with the healthy sheets of skin. She noticed that the skin sheets continued to grow tissue that looked and behaved like skin, but that they were missing certain functions: specifically, they couldn't produce hair or sweat. She surmised that there had to be other sources of stem cells found within the skin that are in charge of producing the hair follicles and sweat glands.

Fuchs and colleagues isolated and identified hair follicle stem cells in the skin, and through their study, also helped confirm predictions that stem cells exist in a state of **frequent cycling**. What this means, is that stem cells can go through cycles of work and rest, whereby there are mechanisms that allow these cells to grow at higher rates when needed, but to also slow down or pause when necessary.

It turns out that these stem cells, found in skin, were an ideal model to study this cycling phenomenon, especially since skin is really good at replacing dead cells, and repairing wounds. Fuchs' work noted how these stem cells could decide when to make new cells and when to stop. For example, she observed that when skin was wounded, stem cells not only became more active, but that they also kept a memory of the wounding, and reacted faster when wounded again.

But why do cells keep this memory? The answer might be in the stem cells' job of repairing wounds. Fuchs' work demonstrated that a wound heals faster if inflicted in a spot that had previously seen inflammation. In essence, the cells' ability to remember might help them do their job quicker.

With so many connections to disease and health,

Sidebar: Because wounds normally produce inflammation, Fuchs did experiments to induce inflammation in the skin and to then look for effects in the cells. Strikingly, cells affected by inflammation showed a great number of changes in how their DNA was packaged. Most of these changes reverted back after inflammation, but many remained like a memory - some of them even after six months. However, this memory also appears to lead to quicker inflammation, which in certain diseases, can result in more damage.

Furthermore, this work might also be important in the fight against cancer. Fuchs currently wonders about the relationship between this disease with wound healing and inflammation.. She explains, "The reason why we became increasingly interested is that every time we generated mice that healed their wounds faster, those mice were also more susceptible to develop tumors". With such intriguing results, Fuchs' team is now actively trying to understand the mechanics of this.

stem cell biology is a truly fascinating and complex field, and Fuchs' discoveries and techniques have been a crucial part of this journey. It is already science that sometimes works like an elixir of life, and further work will continue to lead to new exciting possibilities in human medicine.

Cadherin and Catenin: A Sticky Situation

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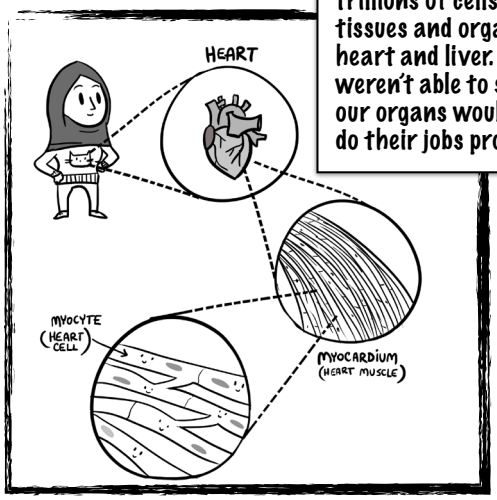

The human body is made up of trillions of cells that form tissues and organs like the heart and liver. If our cells weren't able to stick together, our organs wouldn't be able to do their jobs properly.

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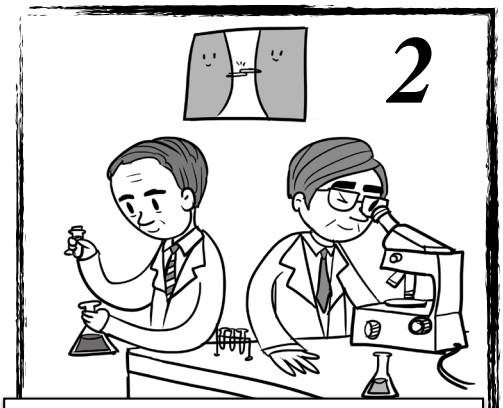

Two scientists named Takeichi Masatoshi and Rolf Kemler discovered that cells stick together by producing a protein called cadherin.

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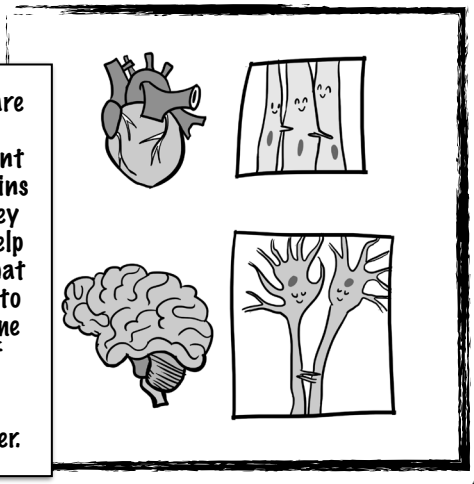

There are many different cadherins and they each help cells that belong to the same type of organ stick together.

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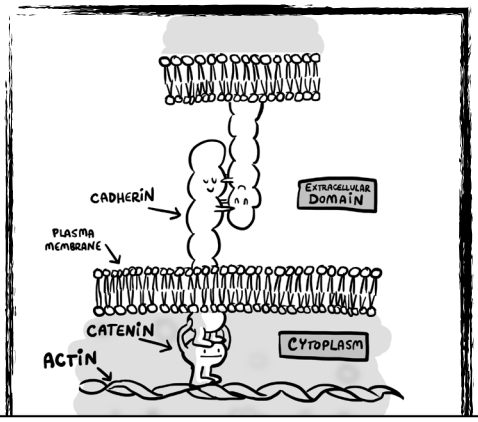

Cadherins make connections with the rigid inner part of a cell, called the cytoskeleton, to help stabilize their contacts. This is actually mediated by another family of proteins called catenins.

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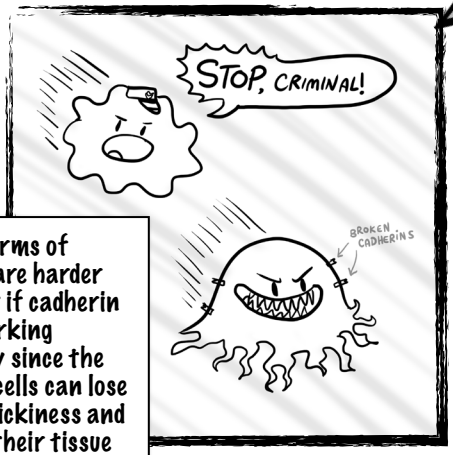


Some forms of cancer are harder to treat if cadherin isn't working properly since the cancer cells can lose their stickiness and escape their tissue of origin.

6

Continuing to study how cadherin works and how it is involved in cancer could help us develop treatment strategies to get people better, faster!

Art by Armin Mortazavi and text by Shawn Shortill. October 2020

Cadherin and Catenins: A Sticky Situation

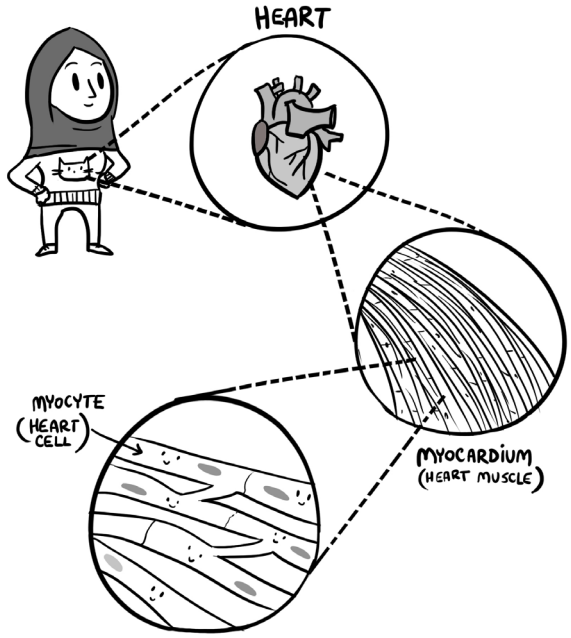
Our cells are able to come together and form tissues and organs by way of specialized proteins that act as a kind of cellular glue.

Written by Shawn Shortill
Art by Armin Mortazavi

October 2020

Have you ever tried to do arts and crafts without glue? Or imagine if you opened a book and all the pages fell out. Turns out that an important ingredient to building things is often a sticky substance to hold it all together, and our own human bodies have taken note of this.

While we are made up of many trillions of cells, they aren't all floating around aimlessly. Instead, many of our cells are purposefully held together to form special structures that we know as tissues which, in turn, come together to form the various organs found in our bodies. Without this level of organization, our organs simply would not work.



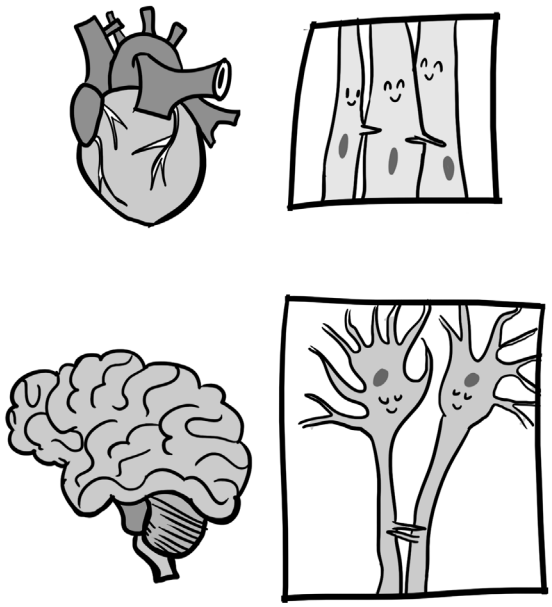
In the mid 1950's, scientists began performing experiments to figure out how similar cell types recognized each other and organized themselves into unique tissues. These early studies hinted that a certain type of protein molecule was responsible for holding cells together, although the identity of the protein remained elusive. It wasn't until the late 1970's that two scientists, Dr. Rolf Kemler and Dr. Masatoshi Takeichi, used clever experimental approaches to identify the culprit responsible for this sticky phenomenon – a calcium-binding cell surface protein that they dubbed **cadherin**.

Takeichi, whose work with cadherin recently earned him a prestigious Canada Gairdner Award, explains: "One important way to study the function of a protein is to observe what would happen in cells or tissues when that function is blocked." Here, Takeichi used **antibodies** (molecules pro-

duced by your immune system that specifically recognize and bind to target proteins) to interfere with or "block" the ability of cells to attach to each other.

In this case, imagine proteins on the surface of cells that are responsible for being sticky. The purpose of the **inhibitory antibody** strategy, is that if an antibody binds to one of these proteins, it effectively blocks the stickiness. And if you find such an antibody, you can also use it to identify the protein. Takeichi basically used this antibody-based approach to identify cadherin.

It quickly became apparent that this was a very important discovery. "The animal body consists of multiple cell types." explains Takeichi. "Individual cells are designed to exert their function only by forming tissues or organs … for example, the heart can pump blood only as a multicellular machine, and the brain can 'think' through multicellular neuronal networks. To generate and maintain these systems, cells need to adhere to each other." With cadherin acknowledged as a cellular adhesion molecule, another important question arose – how do cells of the same type, such as heart cells or neurons, specifically recognize each other to make these tissues?



Continued research efforts using similar antibody-based strategies led to the discovery that cadherin wasn't just a single protein, but was instead a large family of related proteins. It turns out that cadherins consist of multiple types, and that each type of cadherin is produced by a particular group of cells. In this way, cells can adhere to the same type of cells, because they have identical cadherins.

For example, epithelial (or skin) cells will produce the same kind of cadherin, named E-cadherin (named after "epithelium"). Those skin cells will attach very specifically to each other because of their identical cadherin molecule, and in this way form skin tissue. This observation laid the foundation for us to understand how our tissues and organs are put together at the molecular level.

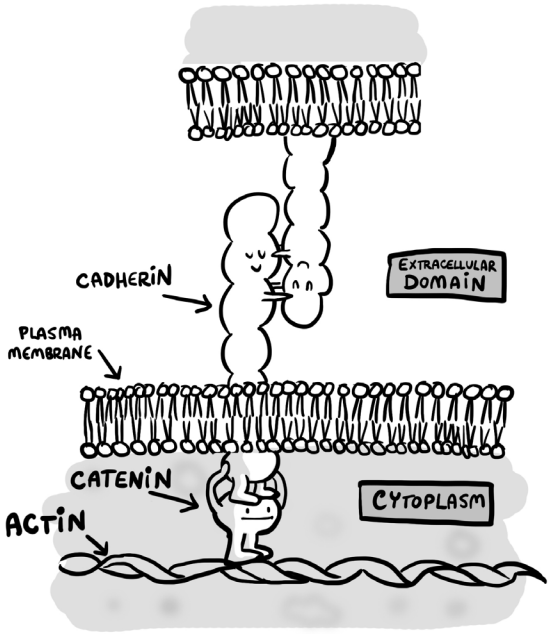
Dr. Rolf Kemler, another recipient of the Canada Gairdner Award, also played an important role in the discovery of the cadherin family. But while it was becoming increasingly clear that cadherins were crucial in the organization of tissues, it would take a few more years and the work of Kemler and his team to unravel the roles of the cadherins in **cellular communication**.

"I grew up on a farm in a little village close to the borders of the former east and west Germany," recalls Kemler. "Because domestic animals were all around, it was natural for me to study veterinary medicine." Here, Kemler developed a keen interest in biology. Eventually, Kemler's scientific interests gravitated towards tissue development and organization and after obtaining his PhD, he began studying cellular adhesion.

Like Takeichi, Kemler and his group used antibodies to seek out the cellular adhesion protein, cadherin. However, in addition to isolating a cadherin protein, Kemler and his team also identified a new protein that was often found attached to cadherins. In doing so, they had unintentionally stumbled upon another important group of proteins known as the **catenin** family. These proteins worked with cadherins to transmit signals from the surrounding environment into the cell in order to promote a biological response.

More specifically, Kemler and his team had discovered an important link between cellular adhesion and the **cytoskeleton** – the filamentous

support network found inside of cells. He explains, "We called these proteins α-catenin, β-catenin, and γ-catenin because, as we later found out, these proteins connect E-cadherin to the actin-based cytoskeletal network."



An important role of the cytoskeleton is to respond to external signals from the environment and help a cell change its shape. Essentially, Kemler's work illuminated the role of cadherins and catenins in how cells would stick together, and how this would also lead to the cells changing their shapes as needed.

These discoveries from both Takeichi, Kemler and their colleagues represented a huge advancement in our understanding of how animals develop from embryos and how organs form. When all is working as intended, groups of cadherins and catenins cooperate and guide cells to organize into multicellular organisms like human beings. However, when cadherin and catenin don't work properly, there can be devastating effects and may even lead to diseases like cancer.

One hypothesis is that the loss of cell adhesion allows a cancer cell to become free from its original tissue and therefore spread to other locations. This process is known as **metastasis**, which often results in a disease being much harder to treat. However, as Takeichi notes, the link between "cadherin or catenin mutations and metastatic behavior of cancer cells is still controversial," making it all the more important that continued study is needed to treat the disease more effectively in the future.

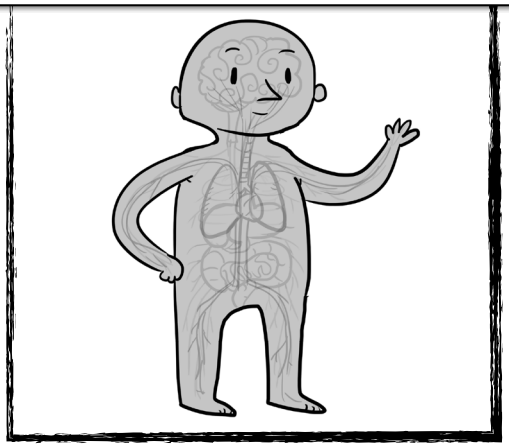
Still, even though we don't have all the answers right now, researchers are optimistic that we may know enough to get started. One strategy involves testing various chemicals for their ability to slow or stop the growth and spread of cancer cells, with known cadherin or catenin defects, in a laboratory setting.

The discoveries of the Canada Gairdner Award winners Masatoshi Takeichi and Rolf Kemler have fundamentally changed the way we think about how cells and tissues organize together and have also given us ideas on how to treat cancer. Their work, like many scientific breakthroughs, has generated as many new questions as it has answered. And with so many exciting questions left open, Takeichi provides a bit of advice. "Curiosity is a key motivation in conducting basic sciences. Ask yourself if you are a person who feels strong curiosity about the strange matters around you. If yes, you should consider becoming a scientist!"

Of Patterns and Cancer in Mice and Flies

1

The human body has many areas of asymmetry: our spines are different than our stomachs, our feet are opposite our heads, even our thumbs demonstrate asymmetry!



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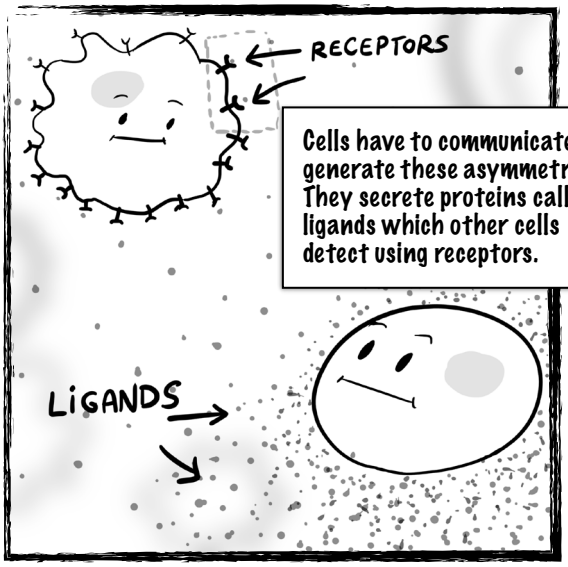

Cells have to communicate to generate these asymmetries. They secrete proteins called ligands which other cells detect using receptors.

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When specific cells send out these ligands, they create a gradient, or differing amounts of ligands in different points. These gradients begin to generate asymmetries throughout development.

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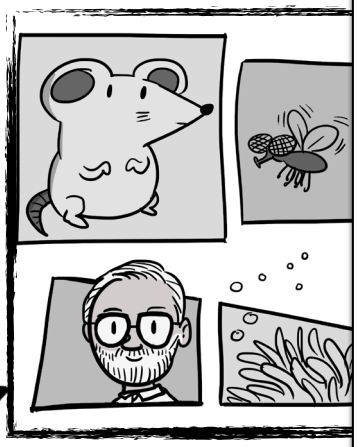

Wnt proteins are one group of ligands important for this process. Dr. Nusse first identified these in mice as contributing to cancer development. They also exist in fruit flies, where they are required for normal wing development, and as early in evolution as sea anemones!

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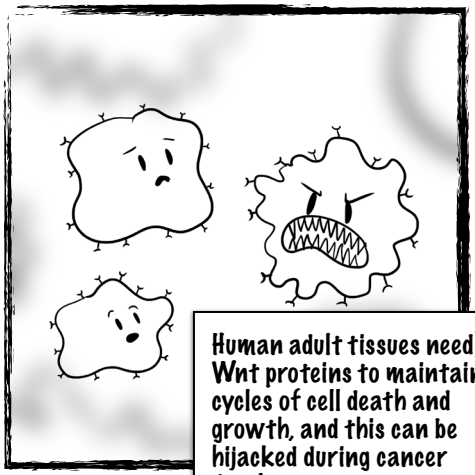

Human adult tissues need Wnt proteins to maintain cycles of cell death and growth, and this can be hijacked during cancer development.

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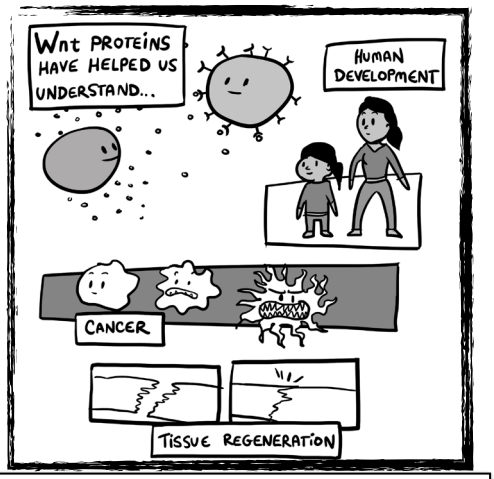


The discovery of Wnt proteins has helped scientists understand human development, cancer, and may even give us some clues about tissue regeneration!

Art by Armin Mortazavi and text by Krysta Coyle. October 2020

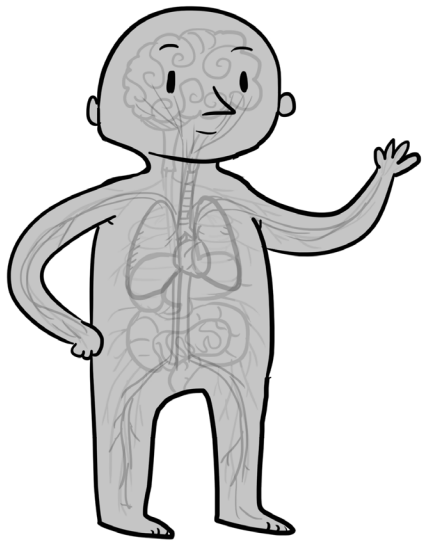
Of Patterns and Cancer in Mice and Flies

The connections between embryonic development and cancer - Dr. Roel Nusse's career in science

Written by Krysta Coyle
Art by Armin Mortazavi

October 2020

When was the last time you mistook the back of someone's head for their face? Hopefully never – because our backs are obviously very different from our fronts. The fact that we have a "front" and a "back" is because we have something called the **dorsoventral axis**. When we were just a single cell (a zygote), we developed into an embryo, and during these early steps (called **embryonic development**), there was a disruption to our symmetry. Ultimately, this change in symmetry allowed all our major organs and structures to develop in their particular places. Things in the front go in the front, and things in the back go in the back. But note that some parts of the human body remain symmetrical – for instance, your left arm and hand are likely a mirror image of your right arm and hand.

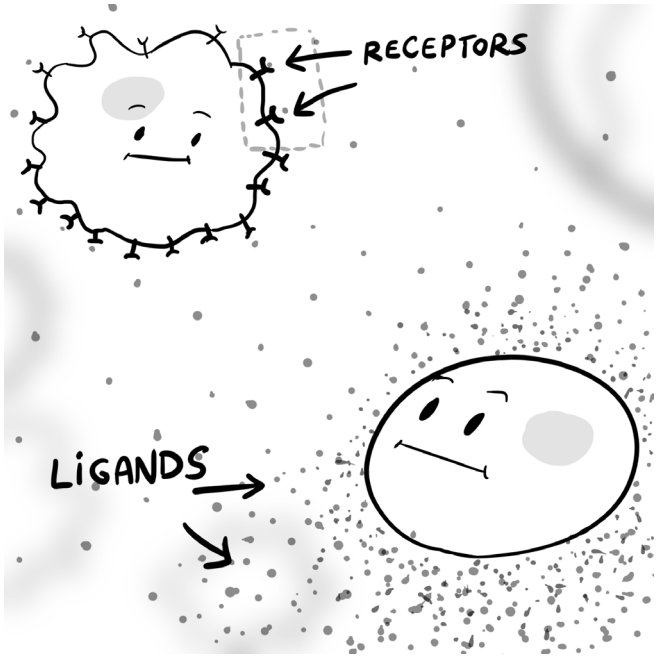


Still, there are all sorts of **asymmetries** throughout the body. The back-to-front asymmetry of the dorsoventral axis is just one example. There's also the top from the bottom, such as how our feet end up at the opposite end from our heads. And don't forget the arrangement of some of the organs inside your torso: your heart is probably on the left side of your body, and your right lung probably has one more lobe than your left lung. If you think about it – even your thumb, which only sticks out of one side of your hand, is a demonstration of asymmetry.

To generate these asymmetric axes, the cells in your body must communicate with each other. This communication is accomplished with a set of proteins, known as **ligands**, that are released from the cells into the space between them (the **extracellular space**). These ligands would then float around looking to interact with other cells who have proteins on their surface known as **receptors**. This interaction between specific ligands and specific receptors essentially allows cells to talk to each other. Think of it as a form of communication, where the cell may interpret an interaction as a signal to turn on or turn off genes. Still, how does this way of communication create asymmetry?

Imagine a cell releasing its ligand. Hopefully, you can see that the concentration of this ligand is going to be highest the closer you are to its source. Conversely, the further away you are, the less ligand there will be. This difference in the amount of ligand forms something known as a **concentration gradient**. In essence, cells can infer their relative position based on where they are located

along this gradient. This difference in the amount of ligands at one end (at one **pole**) of the axis is crucial to the process of asymmetric tissue patterning – there is a gradient that results in the back of our body being different from our front, and a different gradient in determining how our heads become different from our feet.



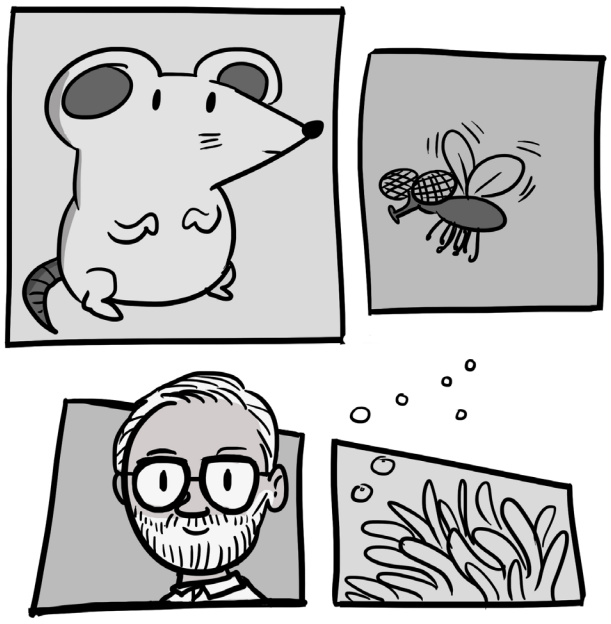
Thanks in large part to the work of Dr. Roel Nusse, we know that an important ligand-receptor in this process is involved in what is known as the **Wnt pathway** (pronounced "wint"). Furthermore, the Wnt pathway is not just crucial for asymmetry and tissue patterning, but it is also involved in the development of cancers. Dr. Nusse is a Professor at Stanford University and has been investigating Wnt signalling for many years.

Like many discoveries in science, the path from cancer to asymmetry was complicated. Initially, Dr. Nusse's PhD work in Amsterdam and postdoctoral work in California focused on understanding how a virus can cause mammary tumors in mice, with the hope of learning more about the origins of human breast cancer. Basically, Dr. Nusse asked, "How can this virus cause cancers?"

Here, he discovered that a virus could insert a copy of its DNA into the host cell. In particular, when the viral DNA is inserted near the mouse gene ***int-1***, it increased the amount of its gene product and contributed to the development of mammary tumors. This breakthrough discovery in breast cancer sparked a long scientific career linking the origins of cancer to embryonic development and to adult tissue maintenance (**homeostasis**).

Later, Dr. Nusse and his colleagues identified that the mouse *int-1* gene was **homologous**, or very closely related, to the *Drosophila* (fruit fly) gene ***wingless***. *Wingless* was aptly named because mutations in this gene could result in fruit flies not having wings. More importantly, *wingless* turned out to be involved in tissue patterning during *Drosophila* development.

With these observations, Dr. Nusse's work helped confirmed that the mechanisms of cell division and embryonic development are remarkably similar throughout the animal kingdom - not only between mice and flies, but even further back in evolutionary time, to the small freshwater hydra and the predatory sea anemones. All of these organisms have genes very similar to *int-1/wingless*, which we now refer to as Wnt. The fact that these Wnt genes are very similar (or **conserved**) between organisms, suggested that they must play important and basic roles in development, growth, and survival.



Looking more closely, humans and other vertebrates have several different Wnt genes. And Dr. Nusse has been intrigued by this gene family for decades. He reiterates, "The most interesting thing

is that the Wnt gene actually encodes a growth factor ligand that is secreted and then interacts with a receptor on another cell." These receptors (called **Frizzled**), when bound to Wnt, pass on a message to the nucleus of a cell, resulting in some genes turning off, and others turning on. Overall, this intercellular communication promotes cell division and provides guidance for tissue patterning. As Dr. Nusse states, "the Wnt pathway is instrumental in making a body plan for multicellular organisms so that we aren't just a mass of cells."

While the Wnt pathway is most important in development, there are some adult tissues that also need Wnt to maintain normal function. For example, Wnt signaling in hair follicles allows for a cycle of hair growth and hair shedding. Our bones also rely on Wnt signaling to keep the proper balance between bone formation by osteoblasts and bone resorption by osteoclasts. "This implicates a function of the Wnt gene in tissues requiring turnover of cells in a measured way."

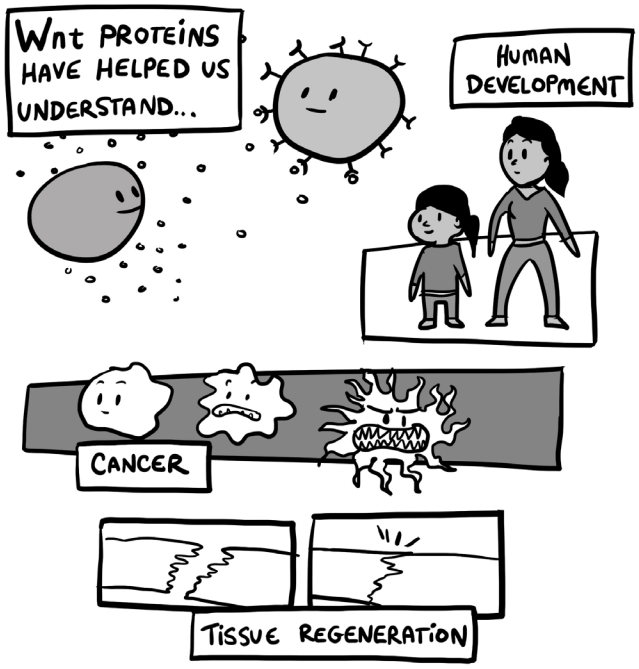
Dr. Nusse reminds us that these mechanisms in normal cells and development are often hijacked as cancer forms. Wnt ligands fundamentally signal a cell to divide, so when a mutation leads to them being inappropriately made and secreted, they can result in increased abnormal levels of cell division, which is one of the hallmark characteristics of cancer.

Dr. Nusse's research connecting a developmental pathway to cancer has laid foundations for numerous research projects around the world. Indeed, many scientists looking for human cancers with Wnt mutations, have instead found other mutations in other communication components of the Wnt pathway - in other words, mutations could exist in a myriad of other proteins that carried the message between the Wnt, Frizzled and the nucleus.

All told, many Wnt pathway genes are mutated in various forms of cancer, including colon cancer, breast cancer, leukemias, and lymphomas. These discoveries, all stemming from Dr. Nusse's work, have led to clinical trials that attempt to control Wnt signaling of tumors, with these specific mutations, to improve the survival of patients.

Sidebar: One of the quickest ways to study how a ligand like Wnt affects cell behaviour is to purify it in large amounts so it can be used in a variety of biological models and systems. Once it is purified, it can also be shared with other researchers, allowing scientific questions to be answered faster than scientists in one laboratory can do on their own. This wasn't easy for Dr. Nusse or his colleagues. Nusse recalls, "One of the most difficult things in my research was purifying the Wnt protein. It took a lot of time and effort and on many occasions, we almost gave up."

Imagine his surprise and excitement when a postdoctoral fellow in his lab succeeded! "I remember clearly, 20 years after those early attempts, when Karl Willert came up to me and showed me that he had purified the protein!" The availability of pure Wnt proteins has helped scientists investigate how they might be used to regenerate or repair damaged tissues. This triumph in the laboratory is one example of how important it is to be persistent in science.



What's next for Dr. Nusse? Currently, he's working on understanding the role Wnt signalling plays in helping repair damaged tissue. His curiosity is infectious, "As always in science, you make one discovery, and another question comes up. There are so many things we don't know that we're still working on!"

From Genes in the Brain to Medicine

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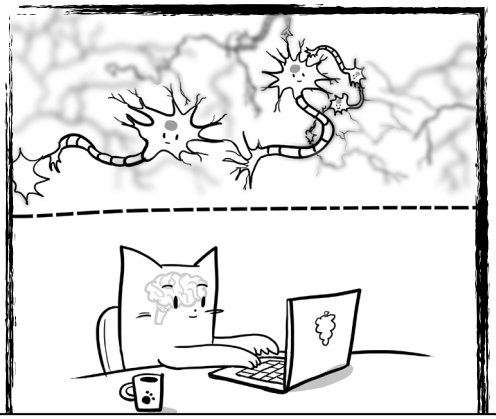

The brain is the control centre of the mind and body. The cells in our brain work together to help us do important tasks like move, see, think, and form memories.

2

If some of the cells in the brain stop working properly, it can lead to brain disorders such as Alzheimer's disease, depression, or amyotrophic lateral sclerosis (ALS). ALS is a disease where the brain loses its ability to communicate with the muscles of the body, resulting in paralysis.

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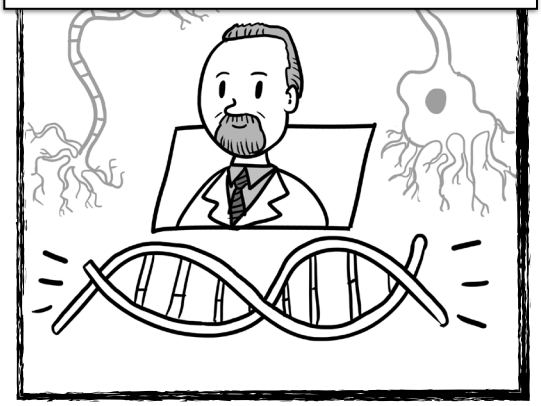
Dr. Guy Rouleau is a scientist and doctor who studies brain diseases like ALS. To figure out what is causing a disease, Rouleau and his team look at the building blocks of biology – genes.



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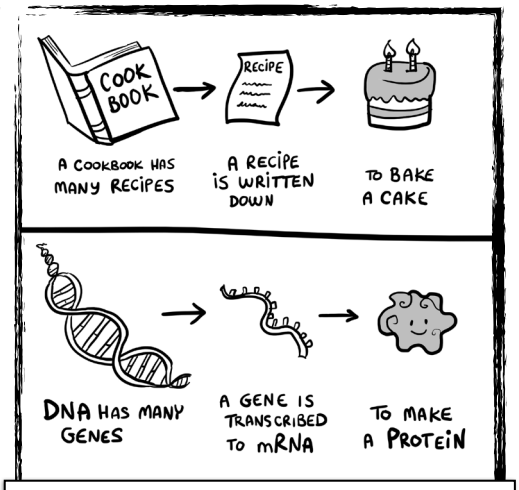

Genes are like biological instruction manuals that tell our cells what to look like and how to function. If a gene becomes mutated, it can cause cells to malfunction and lead to disease.

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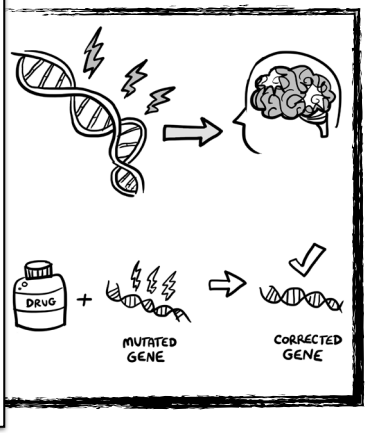
Rouleau has helped identify dozens of genes that cause different brain diseases. Once a gene is identified, treatments can be designed to target the troublesome gene and fix the effects of the mutation. Thanks to Rouleau's work, a drug is now underway to help people with ALS.



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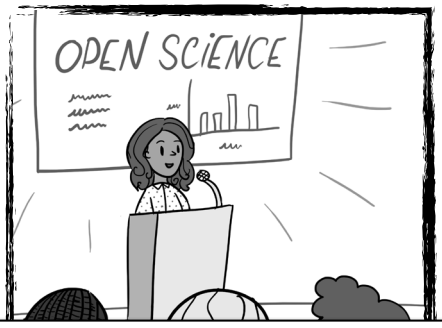


Rouleau is also a big advocate for open science, which is a way of doing science that promotes collaboration and sharing resources between scientists. It is only by working together that scientists can ensure more success stories for brain disease.

Art by Armin Mortazavi and text by Heather Gerrie. October 2020

From Genes to Medicine

Using the building blocks of biology to study and solve complex brain diseases.

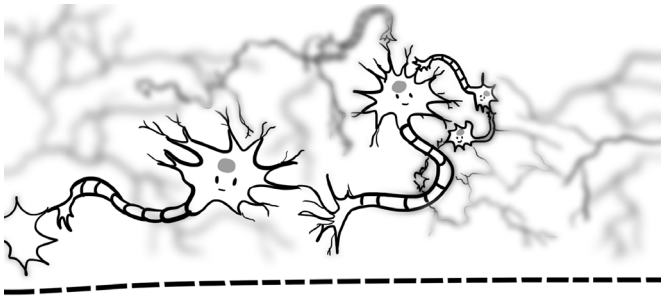
Written by Heather Gerrie
Art by Armin Mortazavi

October 2020

The galaxy in our heads

The brain has been called the most complex object in the universe. It is certainly the most complex organ in the body. Comprised of over 160 billion cells, the brain has more cells than there are stars in the Milky Way galaxy.

All of these cells work together to help the brain with its very complicated task – to act as the control centre of our minds and bodies. The brain receives, organizes, and distributes information for the body, allowing us to interact with the world around us. In order to do this, the brain relies on specialized messenger cells called **neurons**. In the brain, neurons wire together to form intricate circuits and systems. Projecting out of the brain, neurons radiate throughout our bodies as nerves, forming our **nervous system**.



The brain sends information via the nerves to tell our bodies how and when to move, and in turn, receives sensory information – such as sight, smell, or touch – from the nerves. The brain also enables us to think, feel emotions, have a personality, form memories, and learn new skills. In other words, our brains play a role in all of the things that make us human.

The problem of brain disease

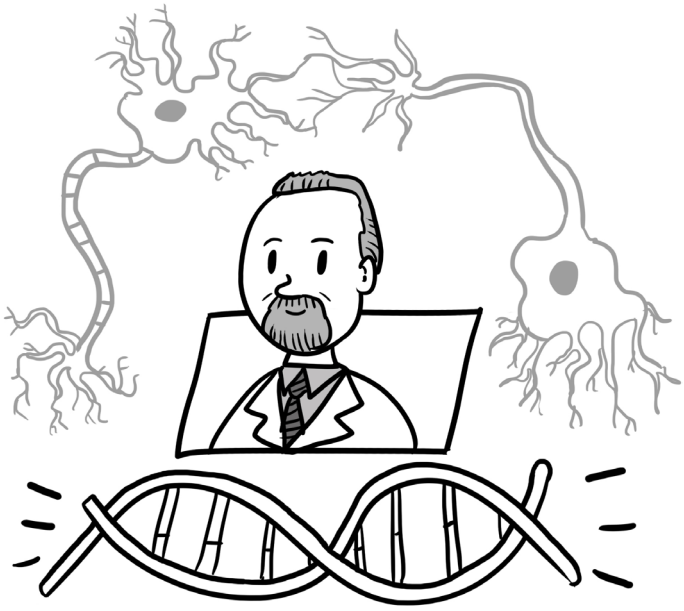
Because the brain has so many important jobs, when something goes wrong in the form of disease or injury, there can be devastating consequences. In Canada, brain disorders are among the leading causes of disability. Approximately one in three Canadians will be affected by a brain disease, disorder, or injury at some point in their lifetime. This includes **Alzheimer's disease, autism spectrum disorder, schizophrenia, depression**, and **concussion.**

Dr. Guy Rouleau is both a **neuroscientist** (a scientist who studies the brain) and a **neurologist** (a doctor who treats brain disorders) who has worked for over three decades to find solutions for diseases that affect the brain and nervous system. As the director of the Montreal Neurological Institute-Hospital (The Neuro), Rouleau knows just how challenging this can be. "The problem with neuroscience is that it's very complicated," says Rouleau. Unfortunately, the complexity that makes the brain so interesting is also what makes it so dif-

ficult to find treatments for brain disorders.

Back to the basics: genetics

So how do scientists solve a problem as complex as human brain disease? For Rouleau, the solution was clear: look at the building blocks of human biology – our genes. "A lot of treatments help a bit or may even help a lot, but they're not targeting the disease," says Rouleau, "but if you find the gene that caused the disease, and if you understand the biology of the disease, you can design treatments that will work."



Rouleau and his team have identified more than 20 genetic risk factors and disease-causing genes for both degenerative and developmental brain disorders – including schizophrenia, autism spectrum disorder, stroke, and epilepsy. To find these troublesome genes, Rouleau looks at the whole genome.

Genomes are similar to instruction manuals. Every living organism has their own genome, which contains all of the unique genetic instructions that make them who they are. Within each genome are many different **genes**, which act like sentences and paragraphs within the manual, each containing their own specific set of instructions. Genes are composed of a chemical code known as **DNA**. If we think of genes as sentences, then DNA provides the letters of the code. When these letters combine to form words, they provide the genetic instructions that tell the cells in our bodies what to look like and how to function.

Sometimes, there is a **mutation** or change in the DNA code of a gene. If we continue to think of DNA as letters, then a mutation can be as simple as a misspelling of a word by a single letter, or as large as a duplication or deletion of whole words or sentences. While not every mutation is bad – some simply have no effect, and some may even be beneficial – some mutations can have very serious consequences.

To find these problematic mutations, Rouleau uses tools such as **single-stranded conformational polymorphism** (SSCP) analysis to locate single-point mutations and the newer technique of **whole genome sequencing**. Whole genome sequencing literally means getting the entire DNA code sequence of an entire genome.

This can be very powerful, as you can compare the different code sequences of different genomes (say between diseased and non-diseased individuals), and look for differences. In turn, these differences may provide clues to the underlying causes of the disease. "With whole genome sequencing you can find all the variants […] all the insertions and deletions, and rearrangements," Rouleau explains. But once a difference, or a mutation has been identified, how does this help people living with brain disorders?

From gene to medicine: a success story

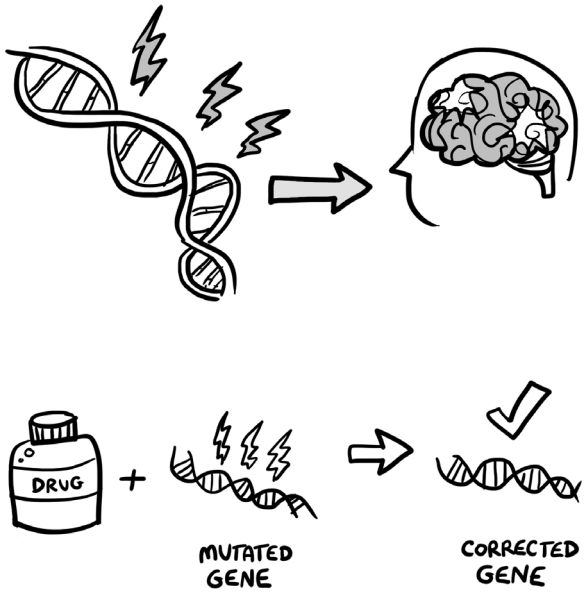
A powerful example of the success of Rouleau's genetic approach is his work on **amyotrophic lateral sclerosis** (ALS). ALS, also known as **Lou Gehrig's Disease**, is a fatal disease where the neurons that control movement begin to die. Over time, this causes the brain to lose its ability to communicate with the muscles of the body, resulting in paralysis.

Rouleau has been researching ALS since 1986. "I was involved in the identification of many of the major genes and have done a lot of work trying to

understand what these genes do and how they lead to ALS," says Rouleau. Eventually, all of his hard work paid off.

In 1993, Rouleau and his team used SSCP analysis to identify mutations in a gene called **SOD1** in a subset of patients with familial ALS. Approximately 5-10% of ALS cases are **familial**, meaning the disease is passed on from a parent to their child. The SOD1 gene is important because it provides the instructions for making the SOD1 protein, a protein which is involved in breaking down toxic molecules. When the SOD1 gene is mutated, this protein does not work properly.

Rouleau explains that by understanding the mutation in the gene, you can reverse or stop the effects of the mutation. This goes beyond simply addressing the symptoms of the disease, to actually finding the root mechanism of why the disease occurred. "If you don't understand the mechanism, it's just a shot in the dark", Rouleau explains, "[When] you understand the mechanism, you can do specific, targeted treatments."



Thanks to Rouleau and his team's efforts, there is now a drug being developed that specifically targets the SOD1 gene to combat the effects of ALS. "It seems to be working spectacularly", says Rouleau, "It will be the first significantly disease modifying treatment in ALS – ever."

Open Science: the way of the future

So how do we ensure more success stories for brain disease? Rouleau strongly believes the way forward should involve the practice of **open science**. Open science is a new approach for conducting scientific research that promotes the sharing of resources, methods, and data between scientists and labs. In Canada, Rouleau has pioneered the practice of open science, and in 2016 he turned The Neuro into the first open science research institute in the world.

While science has always aimed to be a collaborative endeavour, there are several barriers at the systemic or institutional level that can prevent scientists from sharing their resources and data. This includes complicated legal contracts such as patents and material transfer agreements that limit resource sharing, as well as journal paywalls that prevent scientific papers from being freely accessible.

Open science is effective because it removes these obstacles and creates a system where scientists can quickly share their work – both with the public and with other labs. "By sharing freely and sharing quickly, you eliminate barriers to collaboration," says Rouleau. Collaboration is what makes The Neuro such a powerful research institute. When many scientists can work together towards a com-

mon goal, it accelerates scientific discovery.

The hunt for a vaccine for COVID-19 is an example of how effective open science can be. “The [genetic] sequence was available within days, and you have 10,000 scientists studying COVID-19 right now, maybe more,” says Rouleau, “And they can only do that because a lot of the data was freely available […] Instead of taking 10 years to make a vaccine, it might take less than a year.”

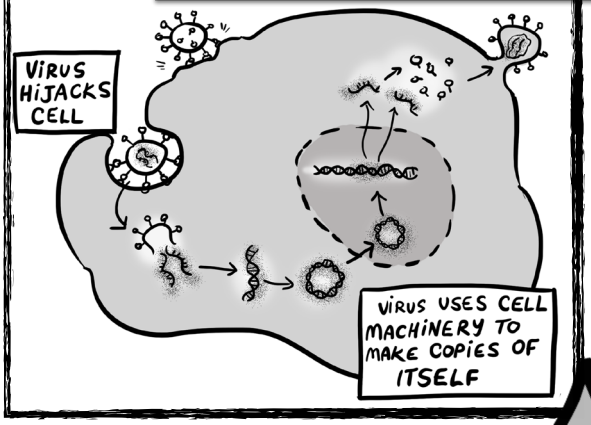
As Rouleau points out, if open science has been so helpful in the case of COVID-19, neuroscientists should adopt the same method of information sharing for brain disease research. “If sharing is accelerating things, why don’t we do the same thing in the rest of medicine?” Rouleau asks. With many scientists tackling the same problem from different perspectives, new treatments and medicine would be available faster.

As Rouleau champions open science – especially as it applies to brain disease – he reminds scientists of the importance of sharing discoveries, “We share freely because [science] should be for the greater good.”

Beyond the ABCs: How to Prevent HIV

1

A virus is a tiny organism which can infect bacteria, plants and animals, causing diseases like the common cold and COVID-19. In humans, one example of a deadly virus is the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome, leaving our body's immune system exposed to other diseases.



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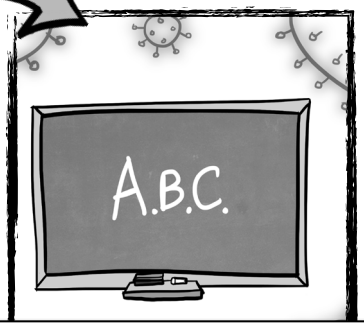
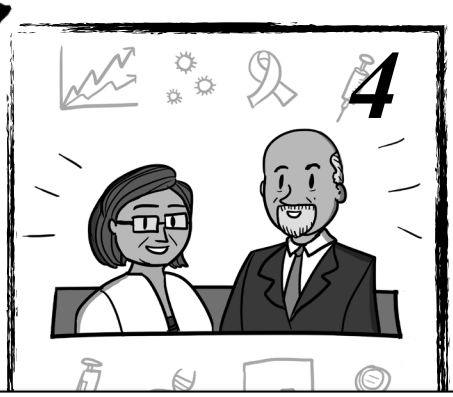


One way to prevent HIV is through the ABCs: abstinence (to avoid having sex), being faithful (to reduce HIV risk by having one partner) and using a condom (to stop the transfer of body fluids).

3

But the ABCs aren't perfect! Are there better ways to prevent HIV, especially for women?

4



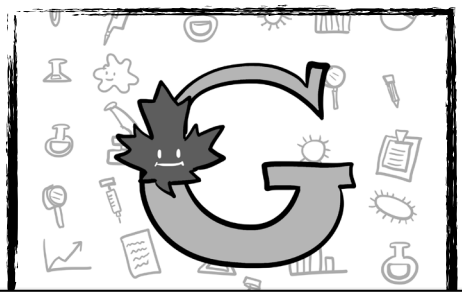
This is what two scientists, Dr. Quarraisha Abdool Karim and Dr. Salim Abdool Karim, have been working on for over 30 years.

The Karims developed, for the first time, a gel which prevents HIV infections through sex, and empowered women to protect themselves.

5

Their work laid the foundations for pre-exposure prophylaxis: a strategy to prevent HIV which is now recommended by the World Health Organization.

6



The Karims are the recipient of a 2020 John Dirks Canada Gairdner Global Health Award for this important contribution. The Gairdner Award is a prestigious honor that recognizes researchers who have made a big impact in their field of study.

Art by Armin Mortazavi and text by Farah Qaiser. October 2020

Beyond the ABCs: How to Prevent HIV

Drs Quarraisha & Salim Abdool Karim developed a gel to prevent sexually acquired HIV infections in women, empowering women to protect themselves

Written by Farah Qaiser
Art by Armin Mortazavi

October 2020

A **virus** is a microscopic organism which consists of a **genome** (genetic material) enclosed within a **capsid** (a protein coat), and sometimes, an additional outer protein **envelope**. Scientists estimate that there are around 10,000,000,000,000,000,000,000,000,000,000 viruses on Earth. That's 31 zeroes…there are a *lot* of viruses!

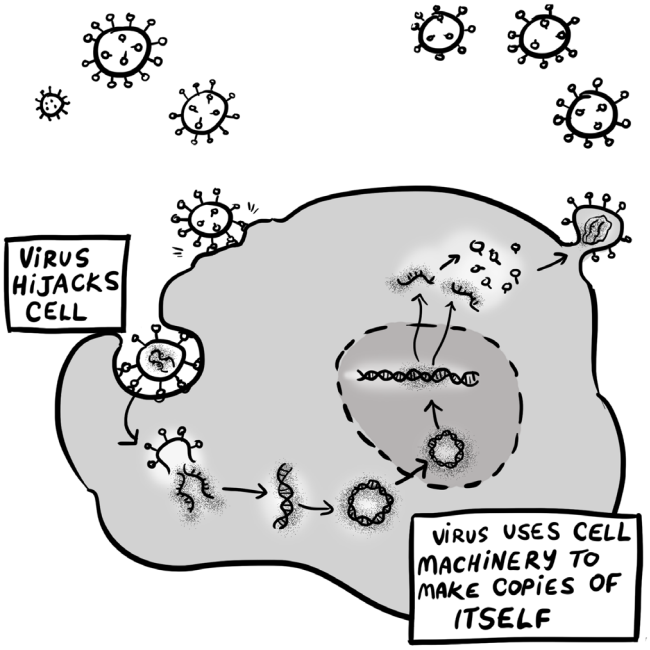
Technically, viruses aren't alive: they can't **reproduce** (make copies of themselves) on their own. Instead, viruses infect living host cells, and multiply in number using the cell's own machinery and resources. These viruses are tiny – instead of being measured in metres or centimetres, they are only **nanometres** (a billionth of a metre) in length. Most viruses are harmless, but some of these miniscule molecular machines can infect living organisms, such as bacteria, plants, and animals, causing diseases like the common cold, rabies, and COVID-19.

In humans, one example of a deadly virus is the **human immunodeficiency virus** (HIV).

Meet HIV: the virus behind AIDS

HIV is a spiky, roughly spherical virus with a diameter of about 120 nanometres. For scale, that's about 60 times smaller than a red blood cell in the human body. HIV also happens to be a **retrovirus**, a type of virus that can insert its genome into the cells it infects.

HIV can only infect CD4+ cells – that is, a cell with a CD4 **receptor** (a type of protein found on the surface of cells). Examples of CD4+ cells include white blood cells, such as **macrophages** (which swallow foreign substances, like cancer cells) and **T-helper cells** (which release **cytokines**, a signalling molecule which activates the immune system). When HIV encounters a CD4+ cell, it binds to the CD4 receptor, fuses with the cell membrane, and releases its genetic material into the host cell.



Unlike the double-stranded DNA found in human cells, HIV's genome consists of single-stranded RNA molecules. Although RNA and DNA are quite similar, they are different in structure, and

consequently for HIV to reproduce, it must use a r**everse transcriptase**, an **enzyme** (a specialized protein), to convert its RNA genome into a DNA version, known as a **provirus**. This provirus then integrates into the host cell's DNA, using a second enzyme called **integrase**. There, the provirus lies dormant, waiting for the host cell to replicate its DNA. Each time the host cell reproduces, it inadvertently produces new HIV particles, which results in two main effects: (1) the host cell is destroyed, and (2) the new HIV particles will go on to infect additional CD4+ cells.

This cycle will continue to repeat again and again. Normally, the human body has between 500 to 1,500 CD4+ cells per cubic millimeter (mm^3) of blood. An HIV infection will steadily weaken the immune system over the years, by causing a drop in the number of CD4+ cells available to fight infections. Eventually, the human body is unable to produce enough new CD4+ cells to replace those being destroyed by HIV.

When there are under 200 CD4+ cells/mm^3, the immune system becomes severely compromised, causing **acquired immunodeficiency syndrome** (AIDS). In this state, the body is more vulnerable to infections that a healthy immune system would be able to fight off, like the common cold and pneumonia, increasing the likelihood of death.

When it comes to preventing HIV/AIDS, the ABCs aren't enough

For decades, researchers have been trying to better understand, prevent and treat HIV/AIDS.

Since HIV spreads largely by the transfer of bodily fluids, such as blood, breast milk, and semen or vaginal fluids during sexual intercourse, experts in Uganda were the first to recommend the **ABCs** to prevent HIV infection: **abstinence** (to avoid having sex), **being faithful** (to reduce exposure to HIV by having a single partner) and using a **condom** (to prevent the transfer of semen).

But the ABCs aren't a perfect HIV prevention strategy, and indeed, have many societal problems associated with them. In fact, two researchers, Dr. Quarraisha Abdool Karim and Dr. Salim Abdool Karim, have been looking beyond the ABCs to prevent HIV infections.

"In 1989, we had good descriptions of AIDS in industrialized countries, and in West, Central and East Africa, but there was very little data on HIV in South Africa," says Dr. Quarraisha, a public health researcher at Centre for the AIDS Programme of Research in South Africa (CAPRISA). "One of the first things in studying epidemics is to understand what the magnitude of the problem is, and its characteristics – who is getting infected by AIDS?"

To answer this question, the Karims carried out population-level surveys to better understand HIV/AIDS in South Africa, and how factors, such as gender and age, played a role in this epidemic.

They quickly learned that women, especially teenagers, were more likely to have HIV infections, and tended to acquire HIV five to seven years earlier than men.

"What became clear was that women understood the risk, but they were unable to negotiate the ABCs – because all of these are dependent on male cooperation," says Dr. Quarraisha, pointing out the gender power imbalance in relationships. In many parts of the world, it can be difficult for

women to insist on following through on the ABCs as they are financially dependant on their sexual partners, an issue that the Karims couldn't directly address through their research.

"We heard this repeatedly [from women]: 'give us something we can use – that is safe and effective.' That's what led us down the path of **microbicides**," says Dr. Quarraisha.

A **microbicide** is a compound that can be applied as a gel or cream inside the vagina or rectum to act as a barrier against sexually transmitted infections, like HIV.

Currently, doctors prescribe a combination of medications to slow down HIV infections, allowing the immune system an opportunity to recover. These medications include the **anti-retroviral** drug, Tenofovir, which slows down HIV reproduction by blocking its reverse transcriptase enzyme. The Karims thought that Tenofovir could be adapted for use in a microbicide, and could potentially be used as a new HIV prevention technology for women.

"We needed to develop a completely new solution because none of the existing solutions addressed the problem," says Dr. Salim, a physician and global health researcher at CAPRISA. "It was a part of Quarraisha's approach: how do we empower women to protect themselves?"

Over two decades, the Karims built a proof-of-concept technology

It took almost two decades for the Karims to finally develop a viable 1% Tenofovir gel microbicide, which women could apply to their vaginas as an HIV prevention strategy. This microbicide was to be taken in two doses: approximately 12 hours before and after sexual intercourse.

The Karims' next step was to test their Tenofovir gel.

"We wanted to do a study that would give us an answer as to whether this gel was safe, and does it prevent HIV? We needed to do the study with enough people to answer both questions," says Dr. Salim.

In 2007, the Karims launched a large-scale study, called CAPRISA 004, to test their Tenofovir gel in over 800 HIV uninfected, sexually active women living in South Africa.

Remarkably, the Karims found that their 1% Tenofovir gel microbicide was 39% effective in reducing the risk of HIV transmission during sexual intercourse. While 39% may not seem like a high number, this was in fact a significant breakthrough. The Karims had demonstrated, for the first time, that Tenofovir gels prevented sexually acquired HIV infections in women, and provided an option for women to protect themselves.

This proof-of-concept was hailed as one of the "Top 10 Scientific Breakthroughs of 2010" in the Science journal, and led the Karims to win multiple awards, including the 2020 John Dirks Canada Gairdner Global Health Award. It also earned the Karims multiple standing ovations at the 2010 XVIII International AIDS Conference.

"Scientists are generally very conservative – they're not a very excitable lot. It's not a rock concert," says Dr. Quarraisha, remembering the very tangible excitement in the air during her talk where she first unveiled their breakthrough findings.

Notably, the Karims' findings laid the foundations for **pre-exposure prophylaxis** (PrEP): a standard HIV prevention strategy that was first recommended by the World Health Organization in 2015, where people at risk for HIV take a daily Tenofo-

vir-containing pill to lower their risk of infection.

Looking ahead

The Karims' long-term vision – trying to stop HIV infections in young women – has not changed since almost thirty years ago. Today, they continue to study different aspects of HIV/AIDS, including the shortcomings of their breakthrough product.

Despite its success, the Karims note that their Tenofovir gel has a low level of efficacy, and its success is highly dependent on women using the gel, which is often difficult to apply. Instead, the Karims are now using a newer, stronger version of Tenofovir, called Tenofovir Elafenamide, to develop an arm implant to place in women, like a contraceptive implant.

"This little tube will release Tenofovir Elafenamide at a very slow level continuously. So, for a whole year, this little implant will be releasing the drug," says Dr. Salim. "We are studying whether this new potent form of Tenofovir, put in an implant, will be more effective in preventing HIV."

The Karims are also studying whether there are additional biological factors which may explain why women had different rates of success with their Tenofovir gel microbicide.

"Science is a very slow process, with incremental knowledge gains," says Dr. Quarraisha. "If you want to be a scientist, you must be persistent, and you must be very passionate about wanting to find the solution. It's not something that will happen instantly. If we knew the answers, we wouldn't need the research."

"If it were easy, everyone else would have already done it. The fact that you take on a difficult problem that does not have an easy solution means that you have to spend years battling through your failures – and how you learn from each failure to do things better the next time, is central to it," says Dr. Salim. "Each failure is one step closer to success."

ACTIVITIES AND DISCUSSION QUESTIONS FOR CLASSROOM USE

By Teri Wang and David Ng

Most suitable for Grades 11 and 12, but some content can also work for Grades 8 to 10. Note that many of the activities are not COVID friendly.

Mina J. Bissell:

Read:

A. McAfee and A. Mortazavi. "**Mammary Gland Mysteries, Solved**" (article, comic and/or video). *Canada Gairdner Awards 2020 Laureates Education Materials,*
pp2 - 6

Learning Objectives:

1. What is cancer?

2. What is the Multihit model?

3. What is the extracellular matrix?

4. What is an organoid?

Supplementary Reading:

Cancer is essentially a disease where cells don't know when to stop multiplying. This leads to uncontrolled growth where cells can become bunched up (tumours), or spread throughout the body (malignancy) - sometimes both. Basically, all of these extra cells can become harmful and even deadly to your body by getting in the way of the important things that normal cells and organs need to do, or even just by crowding things up and taking up too much space. Because cell growth is such a normal part of a cell's life, your body is extra careful in trying to make the occurrence of cancer as difficult as possible.

Normally, the act of a cell growing and dividing is tightly controlled, and usually by way of signals the cell receives. Signals, in this context, generally refer to molecules on the outside (i.e. in the environment) that can interact with proteins on the surface of the cell. Overall, this type of communication system allows a cell to receive cues from the environment, and therefore react accordingly: for instance, should the cell grow or should it stop.

Most folks know that cancer is due to mutations or mistakes in a person's DNA code. This means that mutations can lead to the cell being confused and not responding properly to these signals. For instance, in cancer, the cell may be tricked to think that a growth signal is always "on" which is why it leads to uncontrolled growth. From the article on Dr. Bissell's work, it was also explained that cancer usually requires more than one mutation - in that your body has evolved ways to make getting cancer quite difficult. In science circles, the fact that cancer tends to need more than one mutation is known as the **multihit model**.

The reason for this multihit model makes sense if you think about it. The ability for a cell to grow can be controlled in various ways. For instance: can it get enough nutrients; does it have enough space to grow and divide; and/or will the immune system think that a mass of crazy growing cells looks foreign and try to get rid of it? This means that for a cancer to progress, it may need a mutation that (1) signals for non-stop growth; but also needs mutations that can (2) make sure nutrients and oxygen can get to these cells or (3) mutations that cause the cell to change its surface so

that it remains invisible to the immune system. Note that these are just examples of possible mutations that when accumulated will lead to the cancer disease.

Some of the work that Dr. Mina Bissell is famous for revolves around this idea of signals from the outside (or environment) that can provide additional "hits" in the multihit process. In particular, a lot of her work focused on the extracellular matrix (ECM). Here, you have to think of the outside of cells as not just some vague squishy entity, but actually composed of scaffolds of molecules that allow cells to suspend themselves in specific shapes (it's partly why, for example, your organs look the way they do, and not just some shapeless blob!) In this case, there are particular ligand and receptor systems that are unique to the ECM that can influence the onset of cancer.

Classroom Activity: A game of telestrations and then a discussion period (students can be placed in groups of 6 to 10).

Supplies: paper and pen (if you have the actual boardgame, then the special note pads are also perfect for the activity)

Time: 10 to 15 minutes for activity, 15 minutes for discussion -here, you can break the class up into groups, where each group would try to explain how the game activity illustrates the concepts brought up in the discussion questions 1 to 4 (see below) For instance, Q1 talks about the increased incident of cancer as you age, and that concept could be represented by playing the game longer, resuling in having more cumulative guessing and drawing rounds.

Description: Telestrations is a drawing game that follows the concept of the telephone game. In other words, the first student will be given a phrase (in secret), and then asked to draw it out. The second student will then look at the picture, and attempt to write out (in words) what they think it is. From there, that written guess is then passed onto the next student (who will draw it), and so on and so on and so on.

Purpose: What we hope to see is that the initial phrase will mutate (often in funny ways) to other phrases and concepts. However, what is key is that often the change is incremental (i.e. the phrase might slowly change in minor or logical ways), but at some point can often become completely different from the original phrase. This is to highlight the multihit process - where multiple changes can accumulate to lead to something very drastic outcome (i.e. cancer!)

Discussion Questions:

1. The incident of cancer in an individual is more likely to happen when someone is older. With the background reading and the activity in mind, why does this make sense?

2. In the same vein, sometimes a person is said to be "predisposed" to a certain type of cancer. This means that they have inherited the genetics to have an increased chance of getting cancer, sometimes quite early as well. Again, what do you think this means with the multihit model in mind?

3. One of the most famous signalling proteins that often gets mutated in cancer is known as p53. Basically, in many cancers (including many forms of breast cancer), there is a mistake in this protein that makes it work improperly. Given that p53's primary job is to make sure that the cell's DNA is copied without mistakes, why do you think a broken p53 can be so consequential?

4. Cells often know to stop growing by something known as "contact inhibition." This is probably a term you haven't heard of before, but what do you think it might mean, why is it important in preventing a cell from turning cancerous; and how might the ECM be involved?

5. The article about Dr. Bissell's work also talked about organoids. In terms of testing out medical drugs, why do you think having organoids is so useful?

Elaine Fuchs:

Read:

D. Salas Acosta and A. Mortazavi. "**The Elixir of Life and Our Skin**" (article, comic and/or video). *Canada Gairdner Awards 2020 Laureates Education Materials,* pp7 - 11

Learning Objectives:

1. What are two main features of stem cells?

2. Why are stem cells important?

3. What is reverse genetics?

Supplementary Reading:

Stem cells are like "the jack of all trades" for cells. They have the potential to become all sorts of different cells (see sidebar in the article explaining types of potency). As well, when stem cells divide, they can create more stem cells, all with the same potential ability. However, once a stem cell differentiates, commits, and becomes a specific cell, it can no longer divide into any other cell. It has lost its potency. This is why stem cells have such enormous possibilities in the area of regenerative medicine. If stem cells are ultimately responsible for making our complex cellular structures or are activated to make new cells to replace damaged cells, then it is enticing to wonder how we can use them for medicinal purposes - to essentially grow or repair tissue. Currently, parts of organs and sheets of tissue (like skin) can be grown in a lab from stem cells.

Dr. Fuchs also focused her research on keratin, a protein made by skin stem cells. She discovered that this keratin assembles and organizes in special ways giving our skin the ability to withstand the mechanical stress (rubbing and stretching) of day to day living.

When she introduced DNA mutations into the genetic code of keratin in mice, she noticed that the mouse's skin was more susceptible to damage. Dr. Fuchs saw this and began to wonder whether there were specific skin diseases that were directly related to these keratin mutations. The article outlines how Dr. Fuchs was one of the first to use a strategy called reverse genetics to work this out.

Inflammation of the skin is also a key area of her research. When the skin is wounded, stem cells are activated to help heal the skin. As mentioned in the article, stem cells even keep a memory of that injury so that it can react faster the next time it is wounded.

Classroom Activity 1: Build a "keratin" structure with paper and tape. (students can be placed in groups of 4 to 6).

Supplies: Give each student ten 15x2cm sized strips of paper and 10 cm of tape. Set two chairs or tables 30cm apart. For variation, give some students smaller pieces of paper, or weaker types of paper (toilet paper), less tape, chairs further apart, etc.

Time: 10 to 15 minutes for activity.

Description: Using these materials, students are asked to build a bridge. The bridge that can hold the most weight wins.

Purpose: Different methods of weaving/taping the paper together will tend to result in different strengths even though everyone is using the same materials. This represents the importance of keratin organization to the toughness of skin. Using materials that are different (weaker, etc) can also represent different mutational effects.

Classroom Activity 2: Find the Missing Ingredient! (students can be placed in groups of 4 to 6).

Supplies: Cookie recipe, ingredients, and access to kitchen (at home is fine).

Time: Varied, multiday, although most of the activity occurs at home.

Description: As the teacher, find a cookie recipe and bake a batch where you have deliberately left out one ingredient (your choice). Split your class into groups, and give each group a

small sample of the teacher's cookies. Then, for homework, provide the full recipe (but not telling them which ingredient was skipped), and ask each group to bake a set of cookies where they deliberately leave out one of the ingredients. In one of the subsequent classes, all cookies are to be tried, in an attempt to see if the students can figure out the original missing ingredient.

Purpose: This cooking activity essentially demonstrates the strategy of reverse genetics, where the researcher (cook) deliberately changes a single thing, and then compares the outcome to known diseases (cookie).

Discussion Questions:

1. Doctors often use stem cells to grow sheets of skin for burn victims. What other applications can you think of for stem cells in the medical field?

2. Keratin is one of the components that gives skin its elasticity and strength. Where in our body do you think we would need keratin and where we would not need keratin? Why?

3. Skin stem cells can keep a memory of a past injury so that it can react faster the second time. While good for wound healing, it can often increase inflammation. If you were a stem cell, would you still choose to keep this memory and risk a stronger inflammation reaction to heal wounds faster? Or would you rather heal wounds at a slower rate, but not have bad inflammation? Why?

4. Cancer can be defined as the uncontrollable growth of abnormal cells in the body. Dr. Fuchs' team discovered that mice who were able to heal faster were also more likely to develop cancer! Why might this increased cell regeneration speeds increase the susceptibility to cancer?

Rolf Kemler and Masatoshi Takeichi:

Read:

S. Shortill and A. Mortazavi. "**Cadherin and Catenins: A Sticky Situation**" (article, comic and/or video). *Canada Gairdner Awards 2020 Laureates Education Materials,* pp12 - 15

Learning Objectives:

1. What are cadherins and catenins?

2. What is the cytoskeleton?

3. How are cancer metastasis and cadherins linked?

Supplementary Reading:

As outlined in the article, cadherins are a biological glue keeping cells together. Furthermore, there are different types of cadherins that are highly specific, in that they only stick the right type of cells together. For example, heart cells tend to stick to other heart cells and liver cells stick to other liver cells. Otherwise, without the glue, our body would just be loose cells, but without the specificity, then there wouldn't be the right organizing of cell structures.

Cadherins also work together with proteins called catenins. These catenins connect the cadherins to the cytoskeletal network. The cytoskeleton is the structure that allows cells to maintain their shapes. This connection of the cadherins and catenins to the cytoskeleton essentially means that the stickiness can also coordinate changes in the cells' shapes.

One of the interesting observations that was found when studying cadherins, was that they appeared to play a central role in cancer metastasis. This is essentially a term that denotes the ability of cancer cells to break off from cell structures and then spread throughout the body. This tends to be highly problematic for treatment, as the cancer becomes difficult to pin down. This area is under intensive research and both Dr. Kemler and Dr. Takeichi are interested in finding out more about faulty cadherins. If they are successful in finding treatments that essentially fix faulty cadherin function, this will greatly improve the current standard of care.

Classroom Activity: The Human Knot (students can be placed in groups of about 10).

Supplies: none needed.

Time: 10 to 20 minutes

Description: Each group will form a circle. Each person will then reach forward and randomly join hands with two different people in the circle. The object of the activity is to try and untangle the circle into an open circle, while not letting go of anyone's hands. Do this activity where people are allowed to talk, and where people are not. Do this activity where you are not allowed to "hold" hands, but rather just put them next to each other knuckle to knuckle.

Purpose: The hands linking will represent cadherin molecules sticking together, and the ability to move your arms represents cytoskeletal changes in the cell's shape. The ability to talk, and help direct movement is analogous to the catenins providing that crosstalk. Trying to do the activity by not grasping hands would be similar to a mutational effect where the cadherin binding is flawed.

Discussion Questions:

1. Different cadherins are present on different types of cells. Besides organization, why else might we have different types of cadherins? Do different cells stick together in the same way?

2. The cytoskeleton is what allows the cell to hold different shapes. Why do you think it is important for cells to be able to change their shape?

3. Terry Fox ran across Canada with a prosthetic leg to raise money for cancer. He was initially diagnosed (and appeared to recover) from bone cancer, but then eventually passed away because his cancer had actually metastasized and spread to his lungs. How would drugs affecting cadherin function possibly have changed treat-

ment?

4. When cancer metastasizes, it spreads to different regions of the body. Could some locations in our body be more susceptible to spread? Why might this be?

5. After experiencing a certain disease, our immune system will have antibodies ready that can help fight this specific disease (kind of like the inhibitory antibodies mentioned in the artcle). Could this arsenal of antibodies be taken out and used to help treat others who are infected with that disease (sort of like an inhibitory antibody)? How is this different from how vaccines work?

Roel Nusse:

Read:

K. Coyle and A. Mortazavi. "**Of Patterns and Cancer in Mice and Flies**" (article, comic and/or video). *Canada Gairdner Awards 2020 Laureates Education Materials,* pp16 - 19

Learning Objectives:

1. What is symmetry and asymmetry in embryonic development?

2. What are ligands and receptors?

3. How can mutated genes lead to cancer

Supplementary Reading:

From our hands and feet, to internal organs like kidneys, a lot of our body is symmetrical. However, a lot of our body is also asymmetrical. For example, we have an obvious top and an obvious bottom, as well as asymmetry when looking at the body from back to front. The way our bodies follow a strict pattern is all a result of our cells receiving signals during embryonic development (from zygote to embryo).

As described in the article, cell signaling usually occurs by way of interactions between the environment and the cell. In this context, the outside molecule is often called a ligand, and the molecule on the cell surface is known as a receptor. There are many different ligands, and many different receptors, because there are many different types of signals. When the ligand is bound to the receptor, this will cause more interactions to happen inside the cell, so that the "signal" can make its way to the nucleus (which controls which genes get turned on of off). This is a bit like a line of dominoes falling over in succession: the first tip is the ligand binding, which results in a cascade of signals to the end (the nucleus). Overall, this type of communication system allows a cell to receive cues from the environment, and therefore react accordingly. For instance, should the cell start growing or should it stop: Should it start changing or stay the same. Depending on which ligands are sent out and also the concentration of the ligands (see section on concentration gradients in the article), symmetry or asymmetry of specific cell types and structures can be achieved.

Note that the ligands that cells secrete during development are controlled by our genetics. Dr. Nusse and his team discovered genes coding for ligand and receptor systems that are not just involved in embryonic development, but are also important for cancer development. Essentially, a gene would code for a ligand that instructs other cells to grow at specific places and specific times. But, if there is a mutation or error in this gene, it may result in this careful regulation being faulty, leading to growth of cells at the wrong times and the wrong places. If the growth is uncontrolled, this would lead to cancer.

Knowing the identity of genes and mutations responsible for this faulty activity is very powerful. It allows scientists to develop therapies with specific targets in mind, that can fix the abnormal signals, and possibly treat the cancer itself.

Classroom Activity: Spot the Difference (split the class into 4 groups)

Supplies: Computers and internet connection.

Time: 30 minutes

Description: Ask each group to look for microscopy images of normal versus cancerous cells. When googling, it's best to also include the name of the tissue as well (for instance mammary cells, kidnet cells, lymphocytes, etc). See if the students can notice general differences, although do stress that this can often be very difficult (in truth, it often requires a trained eyed). Examples of abnormalities include more than one nuclei, extra large or dense nuclei, and irregular arrangements of cells. When students have found their images, get them to see if the other groups can identify which is normal versus which is cancerous. After the activity, ask the following questions:

Cancerous cells can look very different from normal cells under a trained eye. What patterns did you notice that are present in all the cancerous cells that made them identifiable?

If you wanted to see whether overstimulation of a specific receptor leads to a cell becoming cancerous and changing its look, how might you design an experiment to test this?

Purpose: this exercise highlights how cancers can often exihibit hallmarks of excess growth, abnormal physical appearance (cells can be undifferentiated), or strange things happening with their nuclei.

Discussion Questions:

1. The gene Wnt codes for protein ligands that promote cell growth. Would scientists want to purify these ligands for medical purposes? Can you think of possible medical outcomes through the use of these ligands- good and/or bad?

2. What other examples of asymmetry and symmetry can you think of in the human body?

3. Top and bottom is an example of asymmetry in plants. Why is it especially important for plants to get this right? What might be the prevailing "signal" that determines up down in plants?

4. How does altering a gene that normally intiates cell growth lead to cancer? How does altering a gene that normally stops cell growth lead to cancer?

5. Many of the genes that exist in human DNA also exist in other organisms. Even in ones where we look nothing alike such as a sea anemone! Why might this be?

Guy Rouleau:

Read:

H. Gerrie and A. Mortazavi. "**From Genes to Medicine"** (article, comic and/or video). *Canada Gairdner Awards 2020 Laureates Education Materials,* pp20 - 24

Learning Objectives:

1. What is amyotrophic lateral sclerosis?

2. What is whole genome sequencing (WGS)?

3. How is WGS used to find genes responsible for diseases?

4. What is open science?

Supplementary Reading:

The brain is the control centre of the body. The neurons that make up the brain relay messages across the body like a messenger system. These messages control everything from what we see and hear, to our emotions and physical movements.

The brain has many diseases and disorders, many of which you have probably heard of. These include diseases such as Huntington's, Alzheimer's, and amyotrophic lateral sclerosis (ALS). Just like how the brain is complex, these diseases are also complex.

However, if we look at what genes are involved in these brain diseases and disorders, we may be able to find ways to fix them. One of the focuses of Dr. Rouleau's research has been on ALS, or Lou Gherig's disease. ALS is a disease that causes weakness and paralysis of the muscles. It does this by damaging motor neurons - the neurons that control movement. As the article describes, Dr. Rouleau's approach relies on whole genome sequencing of healthy patients and comparing them to the whole genomes of patients with ALS. By comparing these differences, he can look for genes responsible for causing this disease.

By understanding which genes are responsible for causing ALS, you can then attempt to design drugs that specifically target the gene. For ALS, one of the genes involved in the disease, is known as SOD1, and treatments that can modify the effects of SOD1, have been shown to alleviate some of the symptoms of ALS.

Dr. Rouleau is also a huge advocate for open science, an approach and philosophy where science research is encouraged to be public and openly shared. This sharing of knowledge between researchers and institutions arguably allows for better collaboration leading to faster scientific discoveries and the democratization of scientific progress.

Classroom Activity: Crunching the Human Genome Numbers (each student can do this individually or in small groups, but then can share their "analogy" at the end of the activity.

Supplies: Computers and internet connection.

Time: 20 minutes and 10 minutes for sharing.

Description: Inform the students that the human genome is approximately 3 billions letters in length. Also tell them that when sequencing this amount of DNA, scientists will usually sequence the genome at least 20 times over to make sure that they are confident in the correctness of the sequence (i.e. minimize chance errors confusing how the code is read). With these numbers in mind, ask the students to come up with analogies that try to showcase just how big these numbers are. An example would be "if you count to 3 billion, 20 times, it would take at least…" Also ask them to create analogies that describes the enormous numbers involved in comparing genomes.

Purpose: This is to show how working with whole genomes is a huge computational task. The numbers involved in whole genome sequencing are kind of crazy, but represent a lot of biological science these days where big data sets are the norm.

Discussion Questions:

1. While complexity is a key reason is why treatment of brain diseases is so difficult, there is also another major reason not necessarily related to genetics. Do you know what that is?

2. Do you think it's possible to compare one genome to another using pen and paper? Do you think that many biologists might also need programming skills these days?

3. ALS affects your motor neurons - the neurons that control muscle movements. How might something that starts as just "clumsiness" end up as life threatening?

4. Do you support open science? Why or why not? Is there any value in keeping science results private?

5. Open science is currently in action during COVID times, where scientific results are published quickly but also often without careful review. What are the pros and cons of this strategy?

Quarraisha & Salim Abdool Karim:

Read:

F. Qaiser and A. Mortazavi. "**Beyond the ABCs: How to Prevent HIV"** (article, comic and/or video). *Canada Gairdner Awards 2020 Laureates Education Materials,* pp25 - 29

Learning Objectives:

1. What is a virus and what is a retroviruses?

2. What is HIV/AIDS?

3. What makes HIV/AIDS difficult to treat?

4. What is a Microbicide and PrEP?

Supplementary Reading:

Our common flu is a virus, our current global pandemic (SARS-CoV-2) is a virus, and the infamous HIV is a virus as well. All three of these have different symptoms and differ in the types of cells they attack, but all share a number of common features. First, viruses are unable to multiply without a host - they can only replicate themselves by using the machinery of a host cell. Furthermore, they are generally very simple entities - basically composed of some genetic code (DNA or RNA) and something that surrounds and protects this genetic material.

The Karims' work focuses on HIV, which is a type of virus known as a retrovirus. Retroviruses use RNA as its starting genetic material, and also produce an enzyme called a reverse transcriptase during infection. This enzyme is special and allows HIV to convert its RNA into DNA, which can then sneakily be integrated into the host cell's DNA. This insertion can hijack the cell, such that it ignores its normal functions, and concentrate primarily on producing more virus. These newly produced virus particles, in turn, spread and begin to take over other cells.

With a normal virus, our immune system often detects the problem and begins to remove the virus, as well as kill the infected cells. However, with HIV, things are a little trickier because HIV actually infects one of the key cells responsible for coordinating that immune response (these are known as CD4+ T cells). As a result, the more the virus spreads, the weaker the immune system becomes. This is why HIV leads to a disease known as Acquired Immunodeficiency Syndrome or AIDS. AIDs patients may have as few as 200 CD4+ cells/mm^3 , where normal numbers would usually approach 500-1200 CD4+ cells/mm^3.

HIV was also difficult to treat because it was very good at mutating, and therefore tended to easily gain resistance against medical drugs. As research has progressed over the decades, we now know that one of the best ways to attack such a virus is to use multiple types of medication at the same time. This has been effective as there is little likelihood of the virus gaining resistance to multiple modes of action at the same time.

For those with the means to afford it, this type of medication (combination antiretroviral therapy) can treat the disease with such success that patients can essentially live their life like a normal person. But for those who cannot afford these drugs, the best treatment might still be prevention. Here, Drs Quarraisha and Salim Abdool Karim were responsible for a crucial part of this strategy, by creating a microbicide gel that can be applied inside the vaginal canal or rectum, acting as a virus killing barrier for at risk women. This gel was 39% effective and led to the start of medical programs focused on pre-exposure prophylaxis (PrEP). PrEP is the HIV prevention strategy where people at high risk of being exposed to HIV can take an antiviral drug every day to lower their chances of infection. This ground breaking idea has prevented countless individuals from spreading and falling ill to this disease.

Classroom Activity: A debate: "Should companies be able to always set their own prices for life saving drugs, such as the ones for HIV/AIDS?"

Supplies: Computers and internet connection for research purposes.

Time: About 30 minutes for the debate (see https://youtu.be/juuiZPQ1ZWk for general structure). Homework time would depend on how

rigorous the teacher would like the debate to be.

Description: Split the class into two teams, and have each team assign three speakers. Arguments would need to be prepared as structured in the above video link. One team will side with "Yes", whilst the other will make a case for "No." Students would need to do some background research first, which can happen either in class or at home. Key terms that may be provided to help with the students research include: access to medicines, pharmaceutical patents, generics, developed versus developing countries, compulsory licenses, HIV medications, Médecins Sans Frontières.

Purpose: This is a great activity to show how scientific research and discoveries often affects society and human rights in significant and nuanced ways.

Discussion Questions:

1. Besides protecting the virus, what else might the capsid around a virus be important?

2. What kinds of proteins (their function) might a virus bring along inside it's capsid besides its genetic information? Why?

3. Why do you think the rate of success of the microbicidal gel is not 100%? How might we change it to make it higher?

4. Why are women the prime targets for the microbicide gel? What does this say about the challenges in gender equity in society?

5. Research online about what antibiotics are used for, and what their targets are. What is the difference between an "antiviral" and an "antibiotic"?

CONTRIBUTORS

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