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"?