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The Canada Gairdner Awards Collection: Celebrating Outstanding Health Researchers

Edited by
Fulvio D'Acquisto and Pasquale Maffia

gairdner
LES PRIX CANADA GAIRDNER AWARDS

ISSN 2296-6846
ISBN 978-2-8325-4600-0
DOI 10.3389/978-2-8325-4600-0

About Frontiers

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About Frontiers for Young Minds

Frontiers for Young Minds believes that the best way to make cutting-edge science discoveries available to younger audiences is to enable young people and scientists to work together to create articles that are both accurate and exciting. That is why distinguished scientists are invited to write about their cutting-edge discoveries in a language that is accessible for young readers, and it is then up to the kids themselves – with the help of a science mentor – to provide feedback and explain to the authors how to best improve the articles before publication. As a result, Frontiers for Young Minds provides a collection of freely available scientific articles by distinguished scientists that are shaped for younger audiences by the input of their own young peers.

What are Frontiers for Young Minds Collections?

A Collection is a series of articles published on a single theme of research and curated by experts in the field. By offering a more comprehensive coverage of perspectives and results around an important subject of research, we hope to provide materials that lead to a higher level of understanding of fundamental science. Alternatively, a collection could feature articles by scientists who received special recognition, such as a Nobel Prize. Frontiers for Young Minds Collections offer our international community of Young Minds access to the latest and most fundamental research; and, most importantly, empowering kids to have their say in how it reaches their peers and the wider public. Every article is peer reviewed according to the Frontiers for Young Minds principles. Find out more on how to host your own Frontiers for Young Minds Collection or contribute to one as an author by contacting the Frontiers Editorial Office: kids@frontiersin.org

The Canada Gairdner Awards Collection: Celebrating Outstanding Health Researchers

Collection editors
Fulvio D'Acquisto — University of Roehampton London, United Kingdom
Pasquale Maffia — University of Glasgow, United Kingdom

Citation
D'Acquisto, F., Maffia, P., eds. (2024). *The Canada Gairdner Awards Collection: Celebrating Outstanding Health Researchers.* Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-4600-0

Cover image
FourPlus Studio

Participating sections

Neuroscience and Psychology

Human Health

About this collection

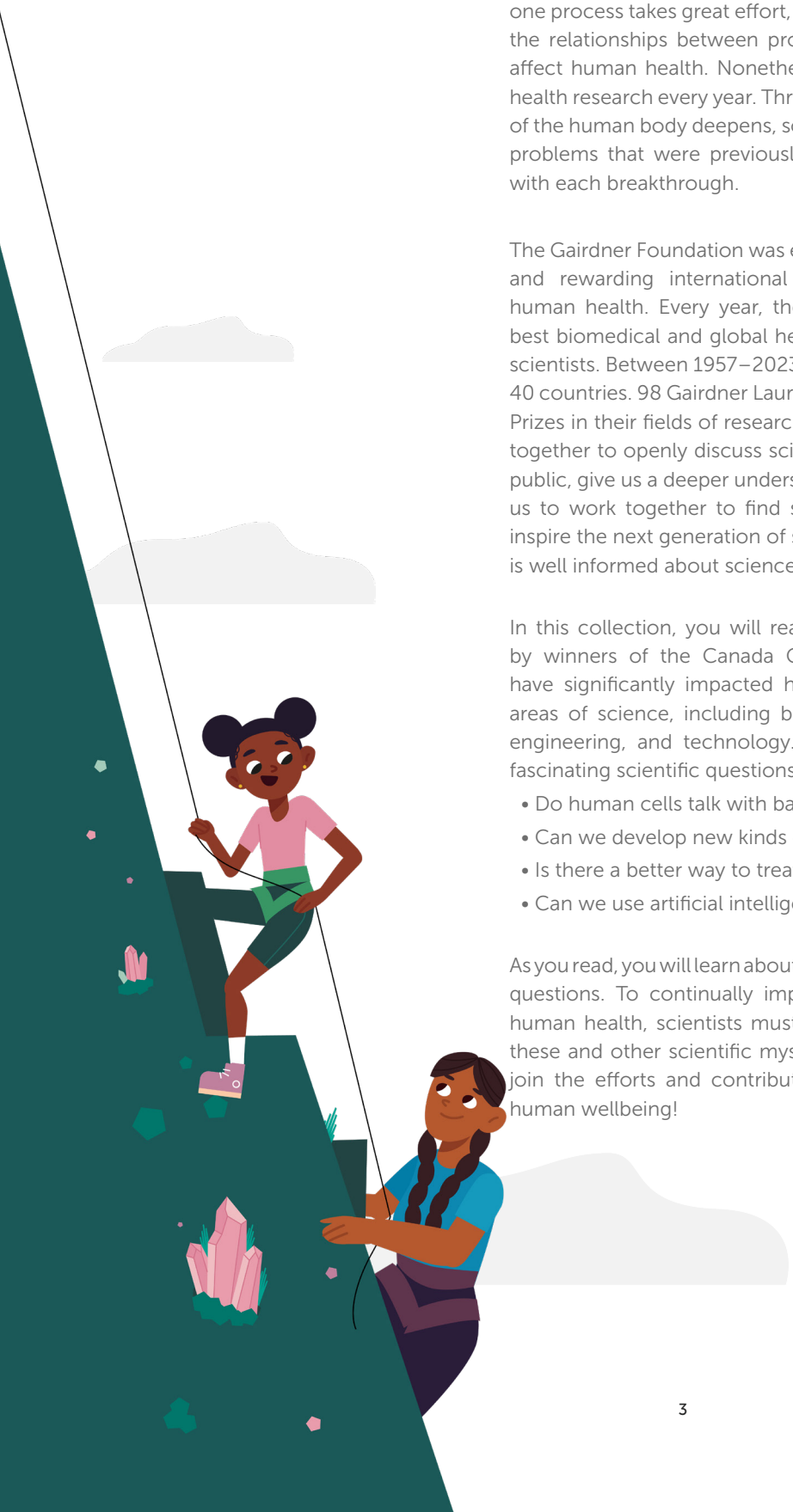
Many great scientists are driven by the desire to understand and improve human health. This is a common desire—we all wish to experience good health throughout our lives, and to receive effective medical treatment if we get injured or sick. Scientists that study health-related questions are leading this journey towards improved human wellbeing. Their jobs are incredibly challenging, because the human body is extremely complex. Countless bodily processes are constantly occurring, all at the same time. Understanding even one process takes great effort, but it is an even bigger challenge to understand the relationships between processes and how these interrelated processes affect human health. Nonetheless, great advances are happening in human health research every year. Through step-by-step research, our understanding of the human body deepens, so that we can eventually manage health-related problems that were previously out of our reach—improving human health with each breakthrough.

The Gairdner Foundation was established in 1957, with the goal of recognizing and rewarding international excellence in basic research that impacts human health. Every year, the Gairdner Foundation celebrates the world's best biomedical and global health researchers by giving eight awards to top scientists. Between 1957–2023, 418 awards were given to scientists from over 40 countries. 98 Gairdner Laureates have subsequently won prestigious Nobel Prizes in their fields of research. The Gairdner Foundation believes in coming together to openly discuss science. Open discussions can better engage the public, give us a deeper understanding of the problems we face, and motivate us to work together to find solutions. The Foundation also works hard to inspire the next generation of scientific innovators and to foster a society that is well informed about science.

In this collection, you will read about some of the great discoveries made by winners of the Canada Gairdner Awards—scientific contributions that have significantly impacted human health. These discoveries span diverse areas of science, including biology, chemistry, biomedicine, neuroscience, engineering, and technology. The articles in this collection will dive into fascinating scientific questions, such as:

- Do human cells talk with bacteria?
- Can we develop new kinds of antibiotics?
- Is there a better way to treat brain tumors?
- Can we use artificial intelligence to speed up medical research?

As you read, you will learn about the newest research addressing these intriguing questions. To continually improve our answers and our understanding of human health, scientists must keep working to deepen their knowledge of these and other scientific mysteries. Hopefully, curious minds like yours will join the efforts and contribute to the meaningful journey toward optimal human wellbeing!



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LES PRIX CANADA GAIRDNER AWARDS

OUR MISSION

The Gairdner Foundation celebrates, informs and inspires scientific excellence around the globe.

The Gairdner Foundation, established in 1957, is dedicated to fulfilling James A. Gairdner's vision to recognize major research contributions to the treatment of disease and alleviation of human suffering. Through annual prestigious Canada Gairdner Awards, the Gairdner Foundation celebrates the world's most creative and accomplished researchers whose work is improving the health and wellbeing of people around the world. Since 1957, 418 awards have been bestowed on laureates from over 40 countries, and of those awardees, 98 have gone on to receive Nobel Prizes.

The Gairdner Foundation believes in coming together to openly discuss science to better engage the public, understand the problems we face, and work together to find solutions. Since its founding, a number of outreach events and programs have been developed with the goal of inspiring the next generation of scientific innovators and fostering an informed society.

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HUMAN HEALTH
Published: 17 October 2023
doi: 10.3389/frym.2023.1241472

AI HELPING SCIENCE: THE 'SHAPE' OF THINGS TO COME

Demis Hassabis * ***and John Jumper***

Google DeepMind, London, United Kingdom

YOUNG REVIEWERS:

GO TEAM
AGE: 15

NEEL
AGE: 12

UMA
AGE: 15

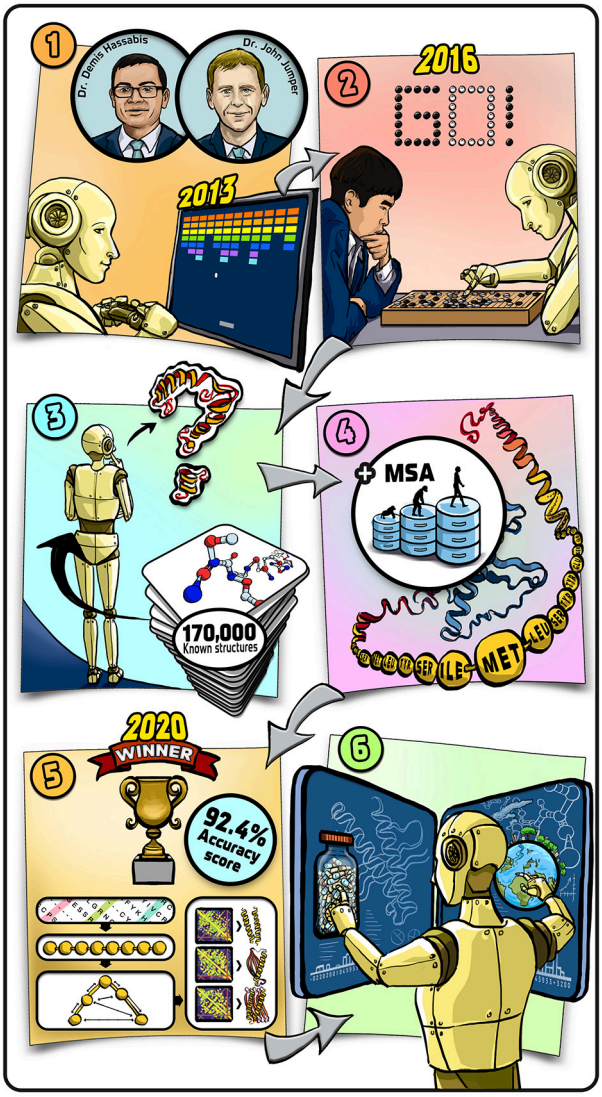
When we started working with artificial intelligence (AI) more than a decade ago, people were skeptical about whether this technology would develop enough in the foreseeable future to do anything useful. But we held on to our faith in AI's potential to benefit humanity. We used games like chess, Go and Atari to train and test our AI systems to become smarter and more capable. In 2016, we decided to use our smart systems to try to solve a 50-year-old fundamental problem in biology, called the protein-folding problem. This was the birth of AlphaFold, our AI system that predicts the three-dimensional structures of proteins based on their amino acid sequence. In this article, you will learn about AlphaFold's achievements, which demonstrate the power of AI to dramatically accelerate scientific discovery and benefit society.

Drs. Demis Hassabis and John Jumper won the 2023 Canada Gairdner International Award for developing AlphaFold,

which is considered to be an AI-based solution to the 50-year grand challenge of predicting the structures of proteins based on their amino acid sequence. AlphaFold has been used to create the most accurate and complete picture of the human proteome—the set of all the proteins in the human body—with enormous potential to accelerate biological and medical research.

Graphical Abstract

(1) We started our journey in 2013 by training our AI systems to play and win classic computer games. **(2)** We then moved to playing more complicated games against real people and, in 2016, our system won a challenge match of *Go* against the reigning world champion. **(3)** Shortly after, we began to tackle the protein-folding problem and trained our system on known protein structures. **(4)** To further train our system, we taught it to use additional databases containing information about how proteins evolved between species. **(5)** In 2020, our system achieved 92.4% average accuracy in the prediction of the three-dimensional structures of proteins. **(6)** We hope that our system will contribute to the development of new drugs, new tools for addressing climate change, and help scientists understand these tiny molecular machines that are the building blocks of life.



Graphical Abstract

PROTEINS

Tiny biological machines that perform most of the actions in our bodies.

THE TINY MACHINES OF LIFE

Did you know that almost all the processes happening in your body are performed by tiny biological machines called **proteins**? Proteins help us to see, to move, to digest food, to fight diseases, and to perform many other essential actions needed to keep organisms like us alive and healthy (to learn more about proteins, check out this video). There

are currently more than 200 million proteins known to science, and new proteins are discovered all the time.

AMINO ACIDS

The building blocks of proteins.

Proteins are made of small building blocks called **amino acids** (to learn more about proteins and their composition, see this video). You can think of a protein like a string of beads, where the amino acids are the beads. There are 20 different amino acids, and they can be arranged in various combinations to make up a protein string. Proteins are made in a "factory" inside cells called the ribosome (to learn more about the ribosome, read this Nobel Collection article). In the ribosome, instructions from our genetic code (our DNA) get translated into chains of amino acids. Then, something amazing happens—these strings of amino acids fold up into complex, three-dimensional structures that in turn determine the functions proteins can perform.

A 50-YEAR-OLD PROBLEM

PROTEIN-FOLDING PROBLEM

A scientific question posed in the 1960s asking how proteins fold to their three-dimensional structure based on their amino acid sequence.

Since the early 1960s, scientists have been trying to understand exactly how the particular sequence of an amino acid chain results in the particular three-dimensional structure of a protein. This is known as the **protein-folding problem** [1]. Because proteins are so important for living things, the protein-folding problem was considered one of the most important problems in biochemistry. When scientists study any protein, they can easily determine which amino acids that protein contains—and even the exact order of amino acids in the protein string. But it has been much more difficult over the years to figure out the final three-dimensional shape that the string of amino acids folds into, to create the working protein machine. After all, proteins are much too small to simply examine under the microscope to see their shapes.

X-RAY CRYSTALLOGRAPHY

An experimental method for determining the three-dimensional structure of protein using X-rays.

To figure out the three-dimensional structure of proteins, scientists have traditionally used a technique called **X-ray crystallography** (Figure 1). This involves crystallizing the protein, which means "freezing" many copies of it in a repeating 3D pattern. The crystallized protein is then examined using a huge machine that bounces high-energy X-rays off the protein (Figure 1A). Finally, the researcher must look at the patterns produced by those X-rays and perform very complex math to interpret the results and determine the actual structure of the protein. This process can take up to a few years for each protein! In the past 50 years, the structures of about 200,000 proteins have been determined by methods like X-ray crystallography, cryo-electron microscopy (to read more about cryo-electron microscopy, see here), and nuclear magnetic resonance analysis, and those structures have been made openly available in the Protein Data Bank.

While this process has been successful, it is clearly too slow and expensive, especially if we want to find *all* the structures of the more

than 200 million proteins that we know of. This is over 1,000 times more proteins than the number of structures we have determined so far!

Why is it so challenging to figure out the final three-dimensional shape of a protein? Well, just like a shoestring, there are an enormous number of ways that a chain of amino acids could potentially fold. Even a small protein, composed of just 150 amino acids, could be in as many as 10^{300} possible configurations (10^{300} is 1 followed by 300 zeroes—that is more than the number of stars in the universe!). With so many possible ways to fold a protein, how could scientists ever know which one is correct without doing time-consuming and expensive experiments like X-ray crystallography?

This is why, at Google DeepMind, we decided to use the power of **artificial intelligence**—the ability of computers to learn from examples and gain insights to solve complex problems—to tackle the protein-folding problem. This approach has proven very useful and saves a lot of time, money, and human effort while also giving us new insights into how proteins work (Figure 1B).

ARTIFICIAL INTELLIGENCE

The ability of computers to learn like the human brain does and mimic human intelligence.

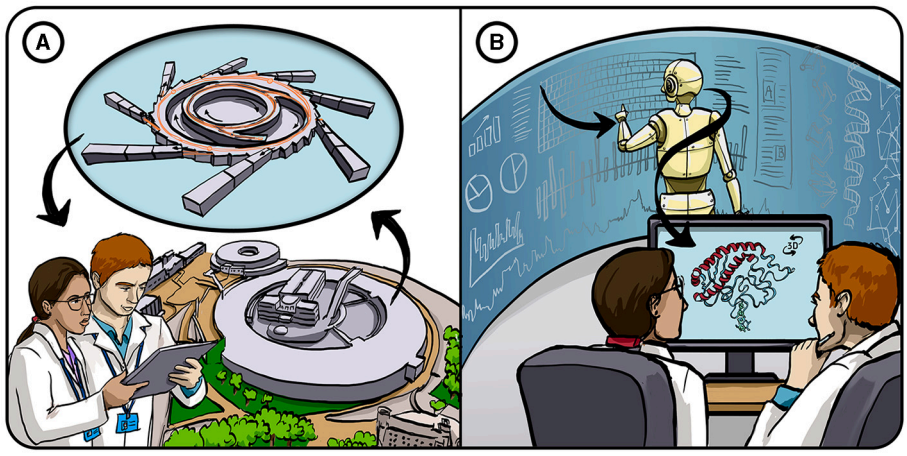


Figure 1

Tackling the protein-folding problem. **(A)** Traditionally, the structure of proteins has been determined by experiments that use very large, expensive machines to bounce X-rays off a crystallized protein (X-ray crystallography), followed by complex math to interpret the results. **(B)** Our approach at Google DeepMind is to use sophisticated AI systems that can use known protein structures and protein databases to learn to predict the structures of proteins that have not been experimentally tested yet. This approach saves a great deal of time and resources.

FROM WINNING GAMES TO SOLVING SCIENTIFIC PROBLEMS

Our approach at Google DeepMind is to combine our passion for AI and our passion for science to find ways for AI to help humanity. At first, we taught our systems how to play simple computer games by teaching them the rules of the games and letting them improve through experience. Our next goal was to make these systems win more complex games, as a steppingstone to tackling difficult real-world problems. This included training an AI model to play a board game called *Go*, which is a very complex game with more than 10^{170} possible board configurations (more than the number of atoms in

the known universe!). For a few years, we developed and tested AI systems in game situations, to see how well they were doing and to keep training them to get better. In 2016, one of our systems called AlphaGo defeated a world champion *Go* player named Lee Sedol—an achievement that was previously considered unimaginable. This was a huge steppingstone, and it proved that our AI systems were smart enough to deal with complex problems.

Google DeepMind has proud roots in scientific research, and so the protein-folding problem was a natural next step for us (Figure 2). Shortly after AlphaGo's achievement in 2016, we assembled a team that started working on predicting the structures of proteins from their amino acid sequences. This new AI system was called AlphaFold (Figure 2A). AlphaFold was designed to learn from existing information about protein structures that had been published in open databases like the Protein Data Bank. Overall, we had access to about 170,000 known protein structures, which we used to train our AI system. We designed AlphaFold to process information somewhat similarly to the way the human brain does, using a computer science idea called artificial neural networks (to learn more about artificial neural networks and machine learning, read this Frontiers for Young Minds article). Like the human brain, AlphaFold can learn from experience and improve its performance. The more examples of protein structures we gave it, the better it got at predicting the structures of new proteins.

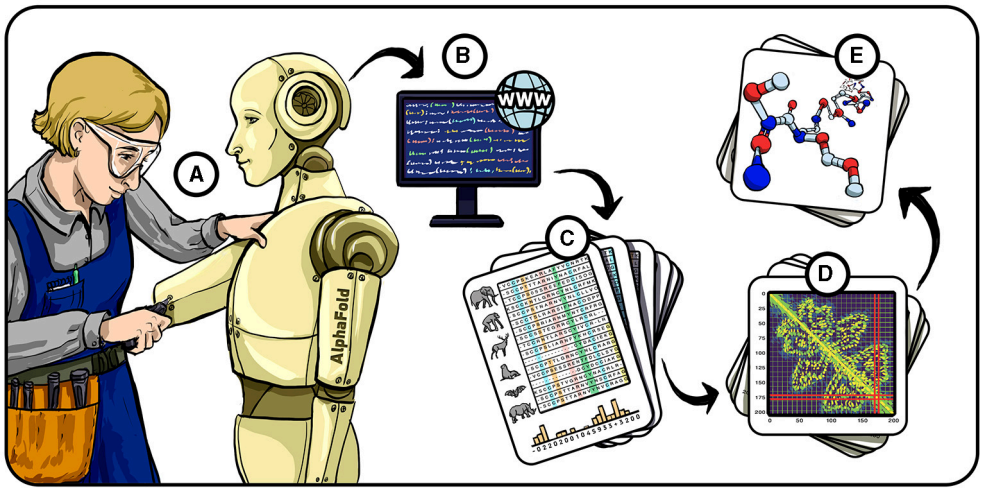


Figure 2

Figure 2

Stages in predicting protein folding. **(A)** In 2016, we started building AlphaFold—our AI system for tackling the protein-folding problem. **(B)** AlphaFold uses information from protein databases to train itself to predict a protein's three-dimensional structure from its amino acid sequence. **(C)** We also trained AlphaFold using MSAs, which are groups of amino acid sequences from proteins that should have a similar structure, based on the functions they perform across multiple different organisms. The amino acids that change together, or "co-evolve," between sequences (colorful columns) carry important information about which amino acids might be close together in the 3D structure. **(D)** Using the input information, AlphaFold predicts the distances and angles between every two amino acids. **(E)** Finally, AlphaFold translates the distances and angles into a predicted three-dimensional structure of the protein.

Unfortunately, even 170,000 examples were not enough to achieve the high level of performance we were looking for—we needed more information to train AlphaFold. So, we used open databases (Figure 2B) containing protein sequences to build what we call **multiple sequence alignments (MSAs**; Figure 2C). An MSA contains sequences that are evolutionarily related to the protein AlphaFold is making a prediction for, and together those sequences contain clues about the structure. The shapes of proteins determine the functions they can perform, and

MULTIPLE SEQUENCE ALIGNMENTS (MSAs)

Amino acid sequences from proteins, found in different organisms, that should have similar structures based on their similar function.

many organisms must perform the same biological function, such as carrying oxygen in the blood. This means that the three-dimensional structures of all oxygen-carrying proteins from different organisms probably stayed similar over the course of evolution, even if their underlying amino acid sequences changed. For that to happen, it means that whenever one amino acid changed in one place in the protein, another amino acid in the protein—the one closest to it in the three-dimensional structure—also had to change accordingly, to preserve the original shape. We call this *co-evolution of amino acids*, and by feeding this information into AlphaFold, we allowed the system to detect hidden relationships between amino acids.

Once we entered enough information into AlphaFold, the system could predict basic information about the shape of a protein, including the distances (Figure 2D) and angles between every two amino acids in the protein and the certainty of the prediction (how reliable it is). This information was "recycled" a few times within the system, and in each round AlphaFold improves its prediction. Finally it uses its basic idea of the protein shape to predict the 3D position of every atom in the protein structure (Figure 2E). When we started, we tested AlphaFold's predictions on proteins whose structures were already known and let AlphaFold improve by learning from its errors and repeatedly correcting itself until its predictions became much better. After it was trained, we used the same network to run on unsolved structures and provide predictions for them.

THE EVOLUTION OF ALPHAFOLD

One exciting milestone in our journey with AlphaFold occurred in 2018, when AlphaFold came first in a biannual protein structure prediction challenge called CASP. AlphaFold received an average accuracy score of around 60 out of 100 on the hardest proteins [2], which was a great leap from the previous best score (which was about 40). This made us even more confident in AlphaFold's capabilities, and we decided to improve the system even further for the next assessment. In our next version, called AlphaFold 2, we incorporated more of our scientific knowledge about the physics and geometry of amino acid chains into the system's learning process and aligned it with everything we understood about the protein-folding problem. Essentially, we taught AlphaFold 2 how to perform MSA analysis, and then used that improved MSA analysis to gain a better understanding of protein folding (and therefore the physics and geometry of amino acid chains). This back-and-forth flow of information improved AlphaFold 2's performance.

In the 2020 CASP14 structure prediction challenge, AlphaFold 2 won with an astounding accuracy score of 92.4 out of 100 [3]. This is approaching the accuracy of determining protein structures using experiments such as X-ray crystallography, but without the high time

commitment or cost. Consequently, AlphaFold 2 was recognized as a solution to the 50-year-old protein-folding problem (see the CASP14 press release).

Even though this was a great achievement, it was still only the beginning. In 2020, we released the predicted protein structures of about 330,000 proteins and, by 2022, we did so for more than 200 million proteins. With time, the knowledge that we gain from all these structures will allow us to better understand protein biology and how proteins work together in cells. This capability will help so many people, from assisting in the development of new drugs and vaccines, to addressing climate change by designing new plastic-eating enzymes [4, 5]. AI systems like AlphaFold 2 could also speed up scientific discovery in general. Imagine how fast science could progress if we harnessed the great learning power of AI systems to tackle difficult problems in *all* fields of science and engineering. These are very exciting times, and we encourage you to stay informed and come along with us on this journey of using AI to unravel the most interesting mysteries of our world!

ADDITIONAL MATERIALS

1. 2023 Canada Gairdner International Award laureates: Dr. Demis Hassabis Dr. John Jumper.
2. Drs. Demis Hassabis and John Jumper–2023 Canada Gairdner International Award (YouTube).
3. Has Protein Folding Been Solved?—Sabine Hossenfelder (YouTube).
4. DeepMind—Homepage.

ACKNOWLEDGMENTS

We wish to thank Noa Segev for conducting the interview which served as the basis for this paper and for co-authoring the paper, and Iris Gat for providing the figures.

REFERENCES

1. Dill, K. A., Ozkan, S. B., Shell, M. S., and Weikl, T. R. 2008. The protein folding problem. *Annu. Rev. Biophys.* 37:289–316. doi: 10.1146/annurev.biophys.37.092707.153558
2. Senior, A. W., Evans, R., Jumper, J., Kirkpatrick, J., Sifre, L., Green, T., et al. 2019. Protein structure prediction using multiple deep neural networks in the 13th Critical Assessment of Protein Structure Prediction (CASP13). *Proteins* 87:1141–8. doi: 10.1002/prot.25834
3. Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., et al. 2021. Applying and improving AlphaFold at CASP14. *Proteins* 89:1711–21. doi: 10.1002/prot.26257

4. Thornton, J. M., Laskowski, R. A., and Borkakoti, N. 2021. AlphaFold heralds a data-driven revolution in biology and medicine. *Nat. Med.* 27:1666–9. doi: 10.1038/s41591-021-01533-0
5. Callaway, E. 2022. What's next for the AI protein-folding revolution. *Nature* 604:234–8. doi: 10.1038/d41586-022-00997-5

SUBMITTED: 26 June 2023; **ACCEPTED:** 07 September 2023;
PUBLISHED ONLINE: 17 October 2023.

EDITOR: Fulvio D'Acquisto, University of Roehampton London, United Kingdom

SCIENCE MENTORS: Sanchita Bhadra and Nicolae Alina-Crenguta

CITATION: Hassabis D and Jumper J (2023) AI Helping Science: The 'Shape' of Things to Come. Front. Young Minds 11:1241472. doi: 10.3389/frym.2023.1241472

CONFLICT OF INTEREST: DH and JJ were employed by Google DeepMind.

YOUNG REVIEWERS

GO TEAM, AGE: 15
The group of reviewers is called GO TEAM and is composed of young children aged 15 who come from several educational centers. It is composed of cheerful teenagers, eager for knowledge and passionate about science. As hobbies, they are passionate about sports such as football and swimming.

NEEL, AGE: 12
Hi my name is Neel. My hobbies are studying and building models of airplanes and cars. I want to become an aerospace engineer in the future.

UMA, AGE: 15
Hi my name is Uma. My hobbies are taekwondo and crochet. I want to become an engineer in the future.

AUTHORS

DEMIS HASSABIS

Demis Hassabis is the co-founder and CEO of Google DeepMind, one of the world's leading AI research groups. Founded in 2010, DeepMind has been at the forefront of the field ever since, producing landmark research breakthroughs such as *AlphaGo*, the first program to beat the world champion at the complex game of Go, and *AlphaFold*, which was heralded as a solution to the 50-year grand challenge of protein folding. A chess and programming child prodigy, Demis reached master standard aged 13 and coded the classic AI simulation game *Theme Park* aged 17. After graduating from Cambridge University in computer science with a double first, he founded pioneering videogames company *Elixir Studios*, and completed a PhD in cognitive neuroscience at UCL investigating memory and imagination processes. His work has been cited over 100,000 times and has featured in *Science's* top 10 Breakthroughs of the Year on 5 separate occasions. He is a Fellow of the Royal Society, and the Royal Academy of Engineering. In 2017 he featured in the *Time 100* list of most influential people, and in 2018 he was awarded a CBE. *press@deepmind.com

JOHN JUMPER

At DeepMind, John Jumper leads the development of new methods to apply machine learning to protein biology. John received his PhD in Chemistry from the University of Chicago, where he developed machine learning methods to simulate protein dynamics. Prior to that, he worked at D.E. Shaw Research on molecular dynamics simulations of protein dynamics and supercooled liquids. He also holds an MPhil in Physics from the University of Cambridge and a B.S. in Physics and Mathematics from Vanderbilt University. John was featured in Nature's 10 people who helped shape science in 2021; find out more here. John and Demis Hassabis co-won the 2023 Breakthrough Prize in Life Sciences.

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HUMAN HEALTH
Published: 17 October 2023
doi: 10.3389/frym.2023.1223179

BACTERIAL QUORUM SENSING: THE MOST ANCIENT LANGUAGE ON EARTH

Bonnie L. Bassler [1,2*], ***E. Peter Greenberg*** [3] ***and Michael R. Silverman*** [4,5]

[1] *Department of Molecular Biology, Princeton University, Princeton, NJ, United States*

[2] *Howard Hughes Medical Institute, Chevy Chase, MD, United States*

[3] *Department of Microbiology, University of Washington, Seattle, WA, United States*

[4] *Emeritus Investigator, The Agouron Institute, La Jolla, CA, United States*

[5] *Emeritus Adjunct Professor, Scripps Institution of Oceanography, University of California, San Diego, San Diego, CA, United States*

YOUNG REVIEWERS:


ANASTASIA
AGE: 15


BRUNA
AGE: 14


HELENA
AGE: 14

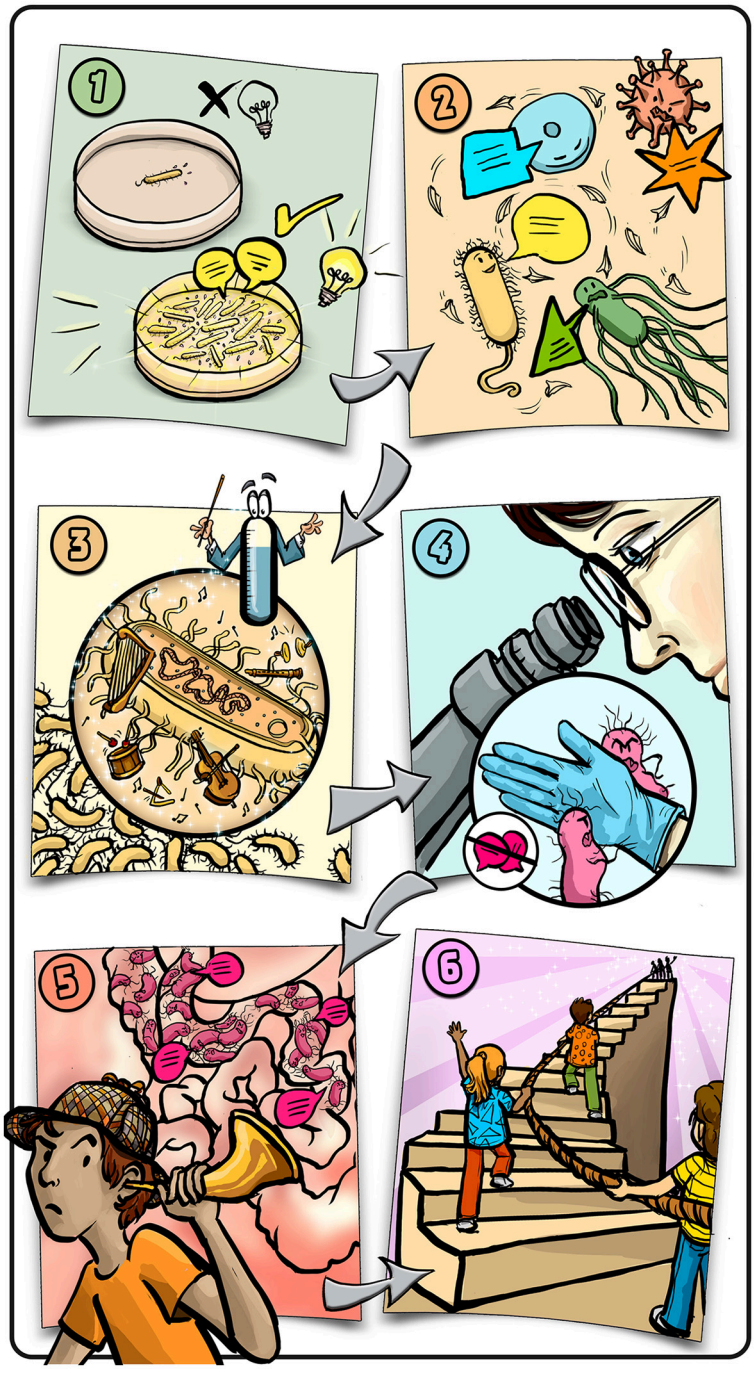

MATHILDE

A few decades ago, scientists believed that bacteria were very basic creatures that did not communicate with each other and were only good at multiplying. Recently, we have realized that this is far from the truth! Bacteria communicate with one another using a language called quorum sensing. You can think of bacterial quorum sensing as the first-ever social network! In this article, we will tell you about the discovery of quorum sensing and how it radically changed our understanding of the microbial world. We will also tell you how our new knowledge of quorum sensing might help doctors to treat dangerous bacterial infections in humans. Join us in this journey exploring the fascinating language of bacteria and how it could benefit human health.

Drs. Bonnie Bassler, Michael Silverman, and E. Peter Greenberg were awarded the 2023 Canada Gairdner International Award for their discoveries of how bacteria communicate with each other and surrounding non-bacterial cells, providing new insights on how microbes behave and opening up exciting directions for developing new drugs against infectious diseases.

Graphical Abstract

Article summary. **(1)** Researchers found that a light-producing bacterium made light only when surrounded by others of its species. They hypothesized that these bacteria produce "chemical words" called "autoinducers" that build up in the environment and trigger light production. **(2)** Further research showed that bacteria use autoinducers to communicate—with themselves, with other species of bacteria, with viruses, and with eukaryotic cells. **(3)** This bacterial communication, called quorum sensing, orchestrates which genes are turned on or off within the bacteria. **(4)** Scientists are developing new treatments for bacterial infections that disrupt the communication of harmful bacteria. **(5)** Knowledge of quorum sensing could help us to "eavesdrop" on the bacterial communication in our bodies. **(6)** It took some decades and many steps to get to where we are, and you can do it, too! Illustration by: Iris Gat.



Graphical Abstract

GLOWING BACTERIA REVEAL AN ANCIENT LANGUAGE

BIOLUMINESCENT

A word that describes a living organism that produces and emits light.

AUTOINDUCER

A chemical that is used in bacterial communication that helps bacteria count other bacteria and other organisms in the environment.

Our story begins with a tiny glowing bacterium. In the 1970s, Ken Nealson and Woody Hastings found that a **bioluminescent** marine bacterium called *Vibrio fischeri* made light only when many bacteria of the same species were close together [1]. These scientists also noticed that, when a large enough group of *V. fischeri* were present, they all started making light at the same time. The scientists hypothesized that the bacteria were producing a chemical called an **autoinducer**, and when there were enough bacteria close to each other, the concentration of the autoinducer got high enough to switch the light on. This was a radical new idea because it meant that bacteria were communicating with each other—these organisms were previously thought to be simplistic "loners" that had no way of communicating.

Then, the three of us (Peter, Mike, and Bonnie) worked for a few decades to uncover the secrets behind this bacterial communication and proved that Ken Nealson and Woody Hastings were right (Box 1). Bacteria constantly communicate and share surprisingly complex information about themselves and their environments—not only with one another, but also with other cells and organisms.

Box 1 | Our main discoveries on bacterial communication.

In the early 1980s, Mike et al. found the genes that were responsible for bioluminescence in *Vibrio fischeri* (Figure 1A) [2]. They showed that when the genes were inserted into other types of bacteria, those bacteria become bioluminescent as well! Later on, Peter took the genes that Mike et al. found and inserted them into a type of bacteria commonly used in research, called *Escherichia coli*, to study the process of bacterial communication [3]. He then showed that other types of bacteria communicate the same way. He also showed that bacterial communication is responsible for **virulence** in a bacterium called *Pseudomonas aeruginosa*, which causes dangerous lung infections in people with diseases like cystic fibrosis (Figure 1B). In 1994, Peter et al. coined the term **quorum sensing** to describe bacterial communication *via* chemical signals, inspired by the legal term quorum, which means the minimal number of people required to attend certain important meetings. Bonnie, who joined Mike's lab in 1990, studied another bioluminescent bacterium called *Vibrio harveyi* and found that it used one autoinducer to communicate with other *V. harveyi* bacteria, and a second autoinducer that turned out to be a "universal" language, shared by many kinds of bacteria [4, 5] (Figure 1C). Bonnie later discovered more types of autoinducers, and that bacteria use these substances to communicate not only with other bacteria but with other organisms, including viruses [6]. She then showed that interfering with quorum sensing could treat certain bacterial infections in animals [7].

VIRULENCE

The ability of bacteria (and other microorganisms) to damage the organisms they infect.

QUORUM SENSING

A type of bacterial communication using chemicals called autoinducers. Quorum sensing is responsible for group behaviors of bacteria, such as bioluminescence and virulence.

QUORUM SENSING—THE WORLD'S EARLIEST COMMUNICATION

Bacteria are the oldest organisms living on Earth. They have about 5,000 genes, and up to 600 of those genes are controlled by quorum sensing. This means that up to one *fourth* of the bacterial genome is like an orchestra that is conducted by quorum sensing. In an orchestra, the conductor does not want all the instruments to play at once—at

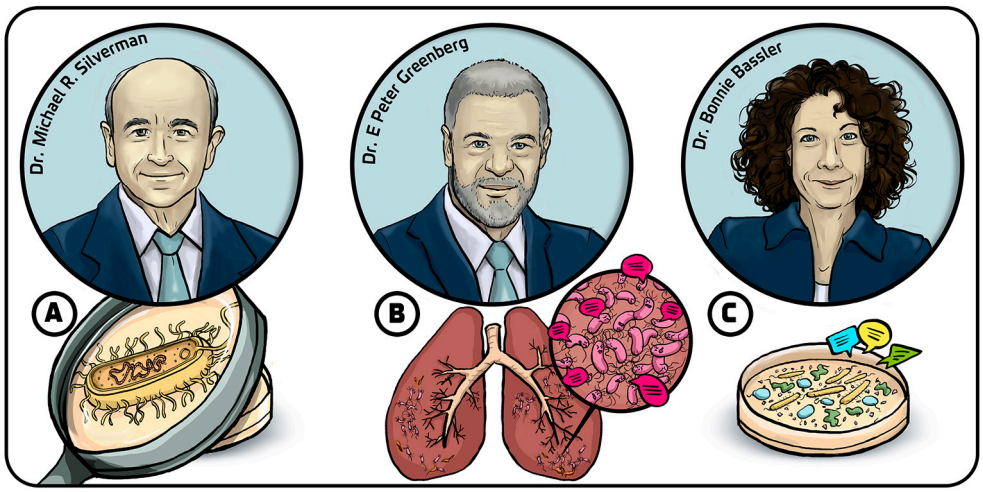


Figure 1

Key discoveries of Drs. Silverman, Greenberg, and Bassler. **(A)** Dr. Silverman found the genes responsible for bioluminescence in *Vibrio fischeri*. **(B)** Dr. Greenberg identified and studied quorum sensing in *Pseudomonas aeruginosa*, which often causes lung infections. **(C)** Dr. Bassler discovered that bacteria communicate using various autoinducers—not only with their own species, but also with other species of bacteria and with viruses. Illustration by: Iris Gat.

a certain moment, she might want the violins to start playing, and at another moment she might want to add the brass instruments. In the bacterial orchestra, the same thing applies: certain gene "instruments" are activated at different autoinducer concentrations. At other times, when autoinducer concentrations are different, some genes might "stop playing" and be switched off.

Quorum sensing was the first communication method to develop on Earth. It is also the earliest social behavior seen on Earth. Bacteria are so tiny that they cannot do much by themselves. But when they use quorum sensing to send and receive information about how many bacteria are around them and about how related they are to each other, they are acting more like a multicellular organism.

We now know that there are at least four types of autoinducers, or "chemical words," in the quorum sensing language (Figure 2). One type is unique in every species of bacteria, and it allows bacteria to communicate with members of their own species. Using this autoinducer, one bacterium can tell another, "you are my twin." Another type of autoinducer is made only by genetically close (but not identical) bacteria, and it says, "you are my relative." A third type is made by many types of bacteria, and basically says, "I am a bacterium." This autoinducer is used to communicate with other species of bacteria. We think that bacteria count the total number of bacteria that are present in their environment. They can even use this third type of autoinducer along with the first type to compute whether their species is the majority or minority in the environment, by dividing the number of "twin" autoinducer molecules by the number of "bacteria" autoinducer molecules. The most recent type of autoinducer discovered is made of two molecules that say, "you are a eukaryote" and "you are a virus." Using these four different "words," bacteria can recognize others of their own species, know

when there are other species of bacteria around, and identify other types of organisms.

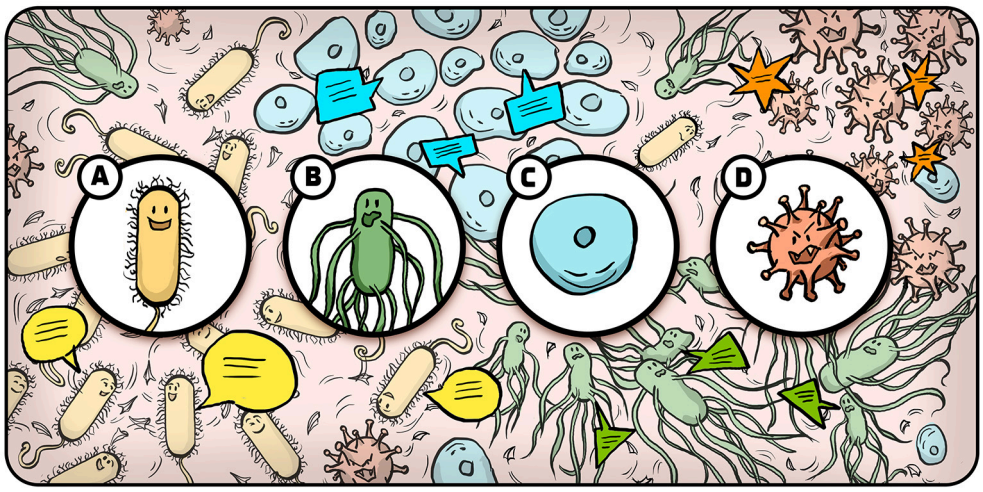


Figure 2

Four types of bacterial communication. Through quorum sensing, bacteria **(A)** talk with other members of their own species, **(B)** communicate with other types of bacteria, **(C)** communicate with eukaryotic cells and **(D)** communicate with viruses. Illustration by: Iris Gat.

NEW ANTIBIOTICS?

Quorum sensing can play an important role in human health, as it is used by harmful, disease-causing bacteria. Disease-causing bacteria have specific genes that make them virulent, and these genes are controlled by quorum sensing. For example, some bacterial genes help bacteria create hard-to-kill communities called **biofilms**, and others help them release their toxins at the right time, to most effectively attack their host. Normally, bacterial infections are treated with antibiotics designed to kill the bacteria or stop them from multiplying. But there are always a few bacteria that are not affected by the antibiotic, and these **antibiotic resistance** bacteria remain alive and keep multiplying within the body (to read more about antibiotic resistance, see this Frontiers for Young Minds article). Might there be another way to neutralize harmful bacteria? Maybe there is a way to disrupt their communication so that they become less harmful?

BIOFILMS

Groups of bacteria that stick to each other and to various surfaces, such as the insides of the intestines.

ANTIBIOTIC RESISTANCE

The trait of bacteria that are insensitive to certain antibiotics and can still multiply in the presence of those drugs.

Scientists are currently working on new antibiotics that prevent bacteria from detecting or producing autoinducers, thereby blocking their communication (Figure 3). When quorum sensing is blocked, bacteria are much less harmful because they can no longer coordinate their harming activities. Unlike "regular" antibiotics, drugs that disrupt quorum sensing do not interfere with bacterial growth and do not kill bacteria, so scientists hope that it will take bacteria much longer to become resistant to antibiotics that target quorum sensing.

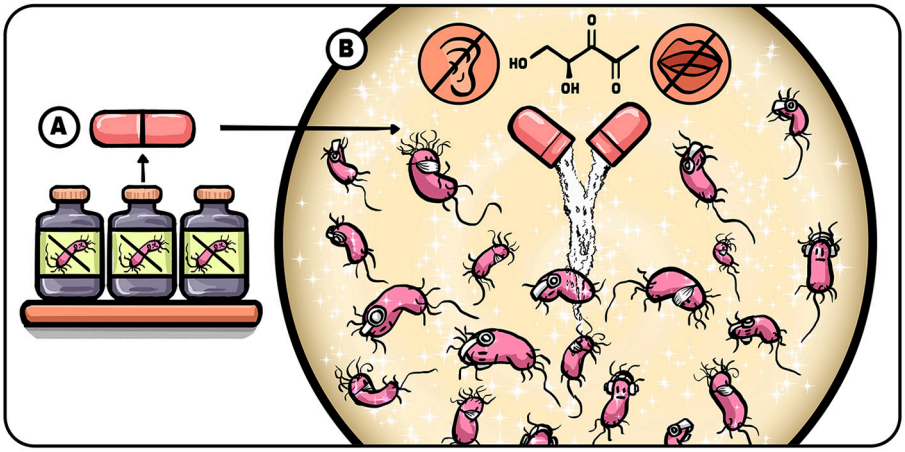


Figure 3

Figure 3

New antibiotics based on quorum sensing. **(A)** Researchers are developing new types of antibiotics based on quorum sensing. **(B)** These antibiotics interfere with the ability of bacteria to communicate, either by making them unable to "talk" to other bacteria (meaning, produce autoinducers), or by making them unable to "hear" what other bacteria are saying (meaning, sense autoinducers in their environment). Illustration by: Iris Gat.

WHAT ELSE CAN WE DO WITH QUORUM SENSING?

Quorum sensing research is developing rapidly, and we keep finding new quorum sensing molecules with very different properties. These molecules may contain more complex information than we initially thought! One fascinating area to study is the communication between bacteria within the human **microbiome**, which is the entire collection of bacteria and other microorganisms in the human body [6]. The human microbiome can communicate with the body, and it is so crucial to the body's healthy functioning that it is now thought of as another organ—even though it is made of non-human cells. For example, the gut microbiome interacts with the immune system and other bodily systems and may even influence mental health. We would like to be able to "eavesdrop" on the interactions between bacteria, and between bacteria and other microbes in the gut microbiome—like investigators listening in on suspects' phone calls. Mapping the communications between organisms in the microbiome might lead to important insights about human health.

MICROBIOME

All the microorganisms that are living in a particular environment, such as the human gut.

We also want to use quorum sensing to study how communities of bacteria cooperate with each other and how they deal with "cheaters" that do not play by the "rules." These cheaters do not help produce necessary substances which the whole community uses, but they still consume them. This makes cheaters more fit than cooperators, because they enjoy these necessary substances without having to invest energy into their production. If being a cheater is so profitable, why do the cheaters not take over the population? It turns out that cheaters do not activate the genes controlled by quorum sensing—which makes them not produce necessary substances, but also makes them vulnerable to a toxin that is released in the population. Cooperators that do activate quorum sensing genes activate a gene that makes them more resistant to this toxin, so they are significantly less affected by it. This is how populations of bacteria maintain

cooperation, and we think we can use this molecular-level knowledge to understand other types of cooperation seen in nature.

LOVING NATURE

The three of us share a great love for nature, and we chose to express this love through science—but there are many other ways to study or work with nature that are also very fulfilling and gratifying. Some of you might want to be doctors; others might enjoy traveling into the jungle and watching exotic animals. Whichever choice connects you with the beauty and wonder of nature is a great path to follow.

If you choose the scientific path, you can view it like a treasure hunt. The "treasures," or big eureka moments that we experience and scientific discoveries that we make, are extremely important and exciting, but they may not happen very often. To find them, we usually work for long periods of time with no positive results. During these times, we must find ways to stay curious and enthusiastic as we "hunt" for the next treasure. Even after we find a treasure, it often takes time for other scientists—or even the scientists who made the discovery—to appreciate what was found. This certainly happened with quorum sensing, and it is frequently the case with any brand new science—it takes time for enough data to accumulate to make an impact. Luckily, we had great colleagues and students that love nature as much as we do, and this made our entire journey fun.

Young people often think that they can never be as successful as we are. The truth is that we were just like you when we were students a few decades ago! It takes time to become a good scientist. We think that any student can become like us, if they stay dedicated to their work for as long as we have been. While it can be useful to have scientific idols that you want to become like 1 day, we also think that, at each stage in your career, you should also choose role models who are closer to where you currently are—these people could serve as steppingstones toward your end goal.

ADDITIONAL MATERIALS

1. How Bacteria "Talk"—Bonnie Bassler (TED)
2. Canada Gairdner International Award Laureates: Drs. Bassler, Greenberg and Silverman

ACKNOWLEDGMENTS

We wish to thank Noa Segev for conducting the interviews which served as the basis for this paper and for co-authoring the paper, and Iris Gat for providing the figures.

REFERENCES

1. Nealson, K. H., Platt, T., and Hastings, J. W. 1970. Cellular control of the synthesis and activity of the bacterial luminescent system. *J. Bacteriol.* 104:313–22. doi: 10.1128/jb.104.1.313-322.1970
2. Engebrecht, J., Nealson, K., and Silverman, M. 1983. Bacterial bioluminescence: isolation and genetic analysis of functions from Vibrio fischeri. *Cell*. 32:773–81. doi: 10.1016/0092-8674(83)90063-6
3. Fuqua, W. C., Winans, S. C., and Greenberg, E. P. 1994. Quorum sensing in bacteria: the LuxR-LuxI family of cell density-responsive transcriptional regulators. *J. Bacteriol.* 176:269–75. doi: 10.1128/jb.176.2.269-275.1994
4. Bassler, B. L., Wright, M., Showalter, R. E., and Silverman, M. R. 1993. Intercellular signalling in Vibrio harveyi: sequence and function of genes regulating expression of luminescence. *Mol. Microbiol.* 9:773–86. doi: 10.1111/j.1365-2958.1993.tb01737.x
5. Chen, X., Schauder, S., Potier, N., Van Dorsselaer, A., Pelczer, I., Bassler, B. L., et al. 2002. Structural identification of a bacterial quorum-sensing signal containing boron. *Nature*. 415:545–9. doi: 10.1038/415545a
6. Duddy, O. P., and Bassler, B. L. 2021. Quorum sensing across bacterial and viral domains. *PLoS Pathog*. 17:e1009074. doi: 10.1371/journal.ppat.1009074
7. Papenfort, K., and Bassler, B. L. 2016. Quorum sensing signal–response systems in Gram-negative bacteria. *Nat. Rev. Microbiol*. 14:576–88. doi: 10.1038/nrmicro.2016.89

SUBMITTED: 15 May 2023; **ACCEPTED:** 31 August 2023;
PUBLISHED ONLINE: 17 October 2023.

EDITOR: Fulvio D'Acquisto, University of Roehampton London, United Kingdom

SCIENCE MENTORS: Sandra R. Maruyama and Alexandra Dimitri

CITATION: Bassler BL, Greenberg EP and Silverman MR (2023) Bacterial Quorum Sensing: The Most Ancient Language on Earth. Front. Young Minds 11:1223179. doi: 10.3389/frym.2023.1223179

CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

ANASTASIA, AGE: 15

I am Anastasia, a student captivated by science! I am very passionate about learning and discovering new opportunities. My dream is to study medicine as I am very interested in how our body works and how it can be affected. Outside of my studies, I love painting, drawing, crafting as well as participating in many other extracurricular clubs. But most of all, I love cooking deserts (I have a sweet tooth ☺).

BRUNA, AGE: 14

I love to play volleyball and basketball, besides watching soccer games. I love to go out with my friends and spend time with my family too. I like to talk and have fun with my little sister, it is good for our relationship. My favorite school subject is math and physics. I really want to have a good health, for example have a healthy eating and do a lot of exercises, I think it is important for young people like us.

HELENA, AGE: 14

I like to do so many things, but there are some activities that I like most. Some of them are playing volleyball, traveling and watching TV shows/concerts. One of the most important things in my life is my family. Also, my dogs. They always make me happy. My life in school is really good. My friends and teachers are so much fun.

MATHILDE

Hi my name is Mathilde and I am going into my senior year of high school in a French school. In my free time I read but can never stick to a book. I also play rugby/ capoeira and wonder where I should study economics and marketing.

AUTHORS

BONNIE L. BASSLER

Bonnie Bassler is a Howard Hughes Medical Institute Investigator and the Squibb Professor and Chair of the Department of Molecular Biology at Princeton University. She grew up in northern California. As a young person, she adored nature and animals and hoped to be a veterinarian when she grew up. However, she became fascinated with biochemistry and molecular biology when she went to college, so she switched direction. Bonnie received a BS in Biochemistry from the University of California at Davis and a PhD in Biochemistry from the Johns Hopkins University. She performed postdoctoral work with Michael Silverman in Genetics at the Agouron Institute. Bonnie joined the Princeton faculty in 1994. Her research focuses on molecular mechanisms that bacteria use for intercellular communication; a process called quorum sensing. Bonnie's discoveries are paving the way to novel therapies to combat disease-causing bacteria. She received prizes including a MacArthur Foundation Fellowship, the Shaw Prize in Life Sciences and Medicine, the Dickson Prize in Medicine, the Gruber Genetics Prize, and the Wolf Prize in Chemistry. Bonnie received Princeton's President's Award for Distinguished Teaching. She is devoted to diversity in the sciences and educating lay people about the thrill and relevance of scientific research. Bonnie was President of the American Society for

Microbiology, and she served on the National Science Board. She was nominated to the Board by President Barack Obama. The Board oversees the NSF and prioritizes the nation's research and educational activities in science, math, and engineering.
*bbassler@princeton.edu

E. PETER GREENBERG

Born November 7, 1948, Hempstead, New York. Education: BA in Biology Western Washington University, 1970; MS Microbiology, University of Iowa, 1972; PhD Microbiology, 1977, University of Massachusetts; Postdoctoral, Harvard University 1977–1978. Academic Positions: Cornell University Assistant Professor Microbiology 1978–1984, Associate Professor Microbiology 1984–1988, University of Iowa Professor of Microbiology 1988–2005 (Shepperd Professor of Microbiology 2000–2005). University of Washington 2005–2008 Professor and Chairman Microbiology, Current position, Nester Professor of Microbiology. Co-Director Microbial Diversity Summer Program, Marine Biological Laboratories, Woods Hole MA, 1985–1990. Major editorial responsibilities: Associate Editor, Annual Reviews of Microbiology, 1987–2001; Editor, Journal of Bacteriology, 1991–2001, Founding Reviewing Editor eLife, 2013–2022; Editorial Board PNAS 2005-present. Selected Honors and Awards: 1984-Elected Member, American Academy of Microbiology, ASM Minority Student Career Support Program, Lecturer: 1989, Elected Fellow, AAAS 1991, Associate Director, University of Iowa Cystic Fibrosis Research Center: 1998-ASM Foundation Lecturer: 2002 Elected Member, American Academy of Arts and Sciences; 2004 Elected Fellow, National Academy of Sciences; 2008, ASM DC White Award 2013, Awarded Honorary Doctorate, University of Guelph; 2015-Shaw Prize in Life Science and Medicine 2017, Honorary Chair North American Cystic Fibrosis Foundation Conference 2022, Clarivate Citation Laureate in Chemistry. Greenberg is widely considered the father of the field of microbial quorum sensing. He has studied quorum sensing since the late 1970s and in fact the term quorum sensing originates in a 1994 *Journal of Bacteriology* article on which he was senior author.

MICHAEL R. SILVERMAN

Mike was born October 7, 1943 in Fort Collins Colorado. He was the son of a rural veterinarian who practiced in western Nebraska, USA. In high school, Mike studied vocational agriculture and later worked on an experimental farm where he developed an interest in plant diseases and bacteriology. He received a BS (1966) and an MS (1968) degree in Bacteriology from the University of Nebraska. In 1972, Mike completed a PhD from the University of California, San Diego studying the molecular genetics of motility and chemotaxis in *Escherichia coli*. This work required the application of classical and modern genetic methods such as DNA cloning and sequencing, gene product programming and transposon mutagenesis. He continued research as an independent scientist at the Agouron Institute and as an Adjunct Professor of marine biology at Scripps Institute of Oceanography in La Jolla California. There, he investigated motility and bioluminescence in marine bacteria. In particular, work with JoAnne Engebrecht and Bonnie Bassler resulted in the discovery of fundamental genetic mechanisms that control bioluminescence. These mechanisms were later found to control many different functions in many species of bacteria. Mike retired to the mountains of Wyoming in 2000.

HUMAN HEALTH
Published: 17 October 2023
doi: 10.3389/frym.2023.1230167

IMPROVING HEALTHCARE FOR PREGNANT WOMEN

José Belizán [1,2*]

[1] *Department of Research in Maternal and Child Health, The Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina*

[2] *Bone Biology Laboratory, School of Medicine, National University of Rosario, Rosario, Argentina*

YOUNG REVIEWERS:

KIYAN
AGE: 14

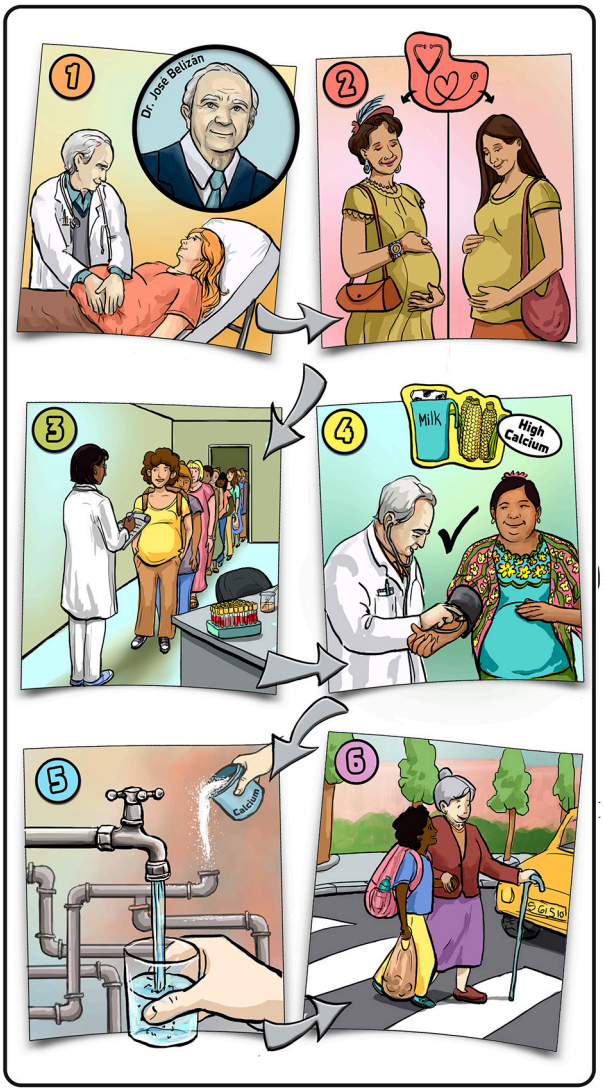
VALENTINA
AGE: 15

I am a medical doctor who treats women during pregnancy and childbirth. I aspire to give them the best possible care, based on scientific evidence. In this article, I will explain how we do scientific experiments in medicine and how we use the results to improve healthcare. I will then tell you about an important relationship I found between calcium intake and high blood pressure in pregnant women, and how this discovery is being used to improve pregnant women's health and even save their lives. Finally, I will share with you some of my hopes for a future of healthcare that is supported by science and benefits everyone.

Dr. José Belizán is the winner of the 2023 John Dirks Canada Gairdner Global Health Award, for his work developing cutting-edge and low-cost treatments for mother and baby health during pregnancy and the first 12 months after childbirth (the "perinatal period"). His work improved wellbeing and care, reduced diseases and deaths, and ensured everyone could benefit equally, including those without healthcare insurance or with low incomes.

Graphical Abstract

(1) I am a doctor taking care of pregnant women. **(2)** I try to provide the best medical care to all pregnant women from all backgrounds. **(3)** I use a scientific process called randomized controlled trials to check whether new treatments can improve upon existing treatments. **(4)** In studies I did in Guatemala, I found a relationship between calcium intake and a dangerous condition that can occur during pregnancy called preeclampsia. Based on my research, experts instructed that most people, and especially pregnant women, should increase their calcium intake. **(5)** One way to increase a population's calcium intake is to add calcium to drinking water. **(6)** For me, helping others is the most gratifying thing I can do.
Illustration by: Iris Gat.



Graphical Abstract

THE ROLE OF DOCTORS

OBSTETRICS

A field of medicine that deals with pregnancy and childbirth.

SOCIO-ECONOMIC STATUS

The life conditions that people experience in terms of their education, income, and quality of life.

EQUITY

The situation in which everyone is treated fairly according to their needs and no group of people is given special treatment.

I am a medical doctor. My specialty is **obstetrics**—throughout my career, I have been trying to provide pregnant women with the best possible healthcare during pregnancy and birth (note: in this article, we use the term "pregnant women" to refer to any person who is carrying a female reproductive system). My role as a doctor is to improve the lives of the people around me and, in some cases, even to save lives. I do that by providing care for patients, easing their pain, and trying to improve the quality of patient care. You might be aware that the **socio-economic status** of people—meaning the life conditions that they have—greatly affects the quality of medical treatment that they normally get. People with high socio-economic status (for example, many people in Canada, the United States, and Europe) usually receive good health care. Unfortunately, people with low socio-economic status (for example, many people in Africa and in Latin America) often do not have access to proper health care. As a doctor treating women in South America, one of my personal missions is to promote **equity** in healthcare and make sure that everyone gets the best possible treatment, irrespective of their socio-economic status.

To provide the best possible treatments to my community, I need to know the needs, wants, and concerns of the population regarding their health and the healthcare they receive. To improve the healthcare that I provide to the women in my population, I first try to find out what bothers them about current healthcare practices. Then I come up with possible changes that could be made to improve existing practices, and I ask the women which of these potential new treatments they might be willing to receive. Finally, before changing the current healthcare practices, I conduct scientific research to check whether the new practice is indeed better than the old one. Importantly, I try to develop procedures that will be inexpensive, so that no woman will be unable to afford proper care.

IMPROVING MEDICAL CARE WITH SCIENCE

When I was a medical student a few decades ago, I was concerned about the quality of medical care provided to women in my community. I noticed that some medical practices and procedures that obstetricians did were uncomfortable or painful for women and were *not* backed up by science (for example, cesarean section as you will see later on). In other words, there was no scientific evidence proving that these practices cause more benefit than harm or that they were better than other practices that might not bother the women as much. In many cases, these procedures became routine just because a well-respected doctor said the procedures work. But one doctor's opinion—no matter how respected that doctor is—is not enough to prove that a certain procedure is better than all other possibilities. Various doctors, myself included, realized that a better,

more scientific method should be developed to measure how well medical procedures work. We wanted to provide medical care based on evidence, not opinions.

Some of us started doing what are called **randomized controlled trials** (Figure 1), which are experiments used to determine scientifically whether a medical practice works [1]. Let us say there is a new drug (or any kind of treatment) that we want to test to see if it should become the common practice for preventing or treating a medical condition. We take a group of people with the medical condition we are studying and assign half of them to receive the new treatment. The other half does not receive the treatment. Importantly, the choice of who receives the treatment and who does not is *random*. In the case of a drug, there is usually one pill that contains the active medicine that we want to test and another pill that looks exactly the same but does not contain the active medicine. The second pill is what we call a **placebo**. None of the people know which pill they are getting, and even the doctor that gives the participants the pills does not know which pills were assigned to which person. After everyone takes the pills for the prescribed time, medical tests are done (for example, measuring blood pressure) and statisticians analyze the data to see if improvements resulted from taking either pill. If statistics show that there were significant improvements among people who took the active pill compared to people who took the placebo, then the new drug is determined to be effective for the disease being studied.

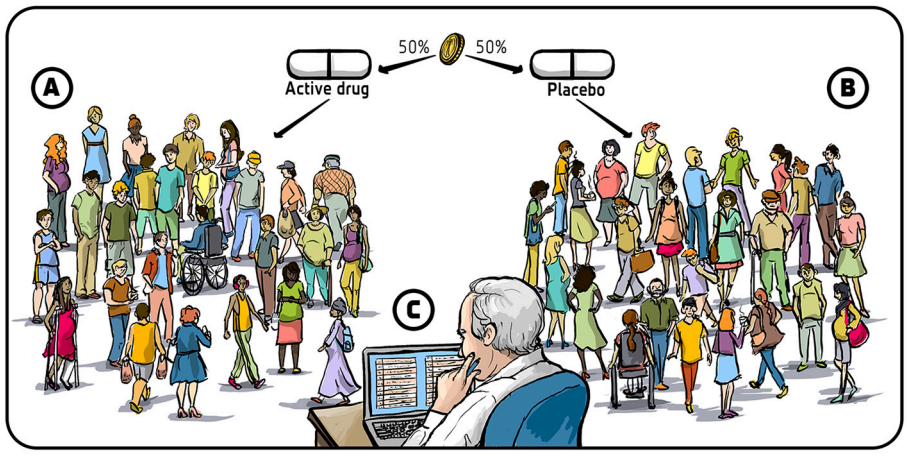


Figure 1

DISCOVERY ABOUT CALCIUM IN PREGNANCY

During pregnancy, some women have a complication called **preeclampsia** [2]. In this condition, the pregnant woman's blood pressure rises during the second half of the pregnancy (Figure 2A). Preeclampsia is a dangerous condition, as it can lead to damage of internal organs of the mother, including the kidneys, liver, lungs, heart,

RANDOMIZED CONTROLLED TRIALS

Experiments in which scientists test new things, like medicines or treatments, by dividing people into two groups and comparing the results fairly to see what works best.

PLACEBO

A pill or treatment given to patients as part of a randomized controlled trial, that does not contain any active medicine.

Figure 1

Randomized controlled trials. In randomized controlled trials, **(A)** a randomly selected half of the tested population is treated with an active drug, and **(B)** the other half is treated with a placebo. **(C)** After the treatment, the data are studied using a type of math called statistics, to see if taking the active drug significantly improved the condition of the patients compared to the group that took the placebo. The drug is only considered a potential new treatment for the condition if its use led to significant improvement. Illustration by: Iris Gat.

PREECLAMPSIA

A dangerous condition that some women experience during pregnancy where they blood pressure rises and could lead to damage of internal organs.

and even the brain. If preeclampsia develops further, it can become an even more dangerous condition called eclampsia, in which pregnant women experience seizures and can die. Until recently, there was no preventive treatment for preeclampsia, and tens of thousands of women around the world died from the condition each year. Doctors knew that giving birth to the child could cure preeclampsia, but in many cases the preeclampsia happened too early in the pregnancy, when the baby was too premature to be born safely.

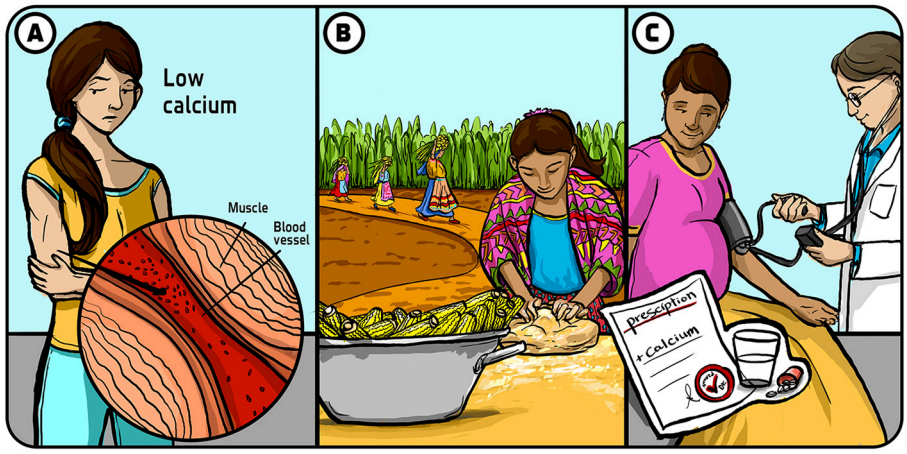


Figure 2

Figure 2

Calcium intake and health. **(A)** When calcium intake is low, the body sends a message to the cells to store what little calcium is taken in with food. When muscles store calcium, they contract and squeeze the blood vessels they surround, increasing blood pressure. **(B)** When I worked in Guatemala, I noticed that pregnant women there rarely experienced preeclampsia during pregnancy. After some studies, I found that these women had high calcium intake because their diets were based on lime treated corn. **(C)** As a result of my studies, it has now become standard for pregnant women to be supplemented with calcium during pregnancy. Illustration by: Iris Gat.

In the 1970s, I was working in Guatemala in Central America. I noticed preeclampsia occurred only rarely among Guatemalan women, much less often than among women with the same socio-economic status from other countries. That surprised me because many of these women were poor and did not have access to good medical care. As I started to study this interesting observation, I realized that the Guatemalan women were eating a Mayan diet that was heavily based on corn (Figure 2B) [3]. Treatment of corn before milling implied soaking corn in lime water resulting in a high concentration of calcium, so I wondered if there could be a relationship between calcium intake and preeclampsia. To test this, my colleagues and I conducted randomized controlled trials where we measured women's calcium intake and eventually proved that women who took extra calcium during pregnancy had a significantly lower risk of suffering from preeclampsia (Figure 2C) [4]. Over time, many other researchers replicated our results and eventually—after professional discussions by a group of experts—the World Health Organization made a strong recommendation that pregnant women should be supplemented with calcium to prevent preeclampsia.

We now know that when there is not enough calcium in the body, a message is sent to the cells to store up the calcium they *do* have. This means that the muscles, including those surrounding blood vessels, take in the calcium that is eaten in food. When muscles take in calcium they contract more, and these contractions squeeze the blood vessels,

leading to an increase in blood pressure. On the contrary, if there is too much calcium in the blood it is removed from the body through urine and does not cause any problems.

There are several reasons why people, specifically pregnant women, might not get enough calcium. One reason is that, for many people, calcium is not available in their diets. About three billion people around the world do not have access to foods containing sufficient amounts of calcium. Even in places where calcium-containing foods *are* available, it can be very difficult to get people to eat enough of these calcium-rich foods, even if they are recommended by experts. Also, sometimes the media leads people to have a specific perception about certain foods. For example, in the US, there was a trend against consuming milk. The argument was that many people experience digestion issues from consuming lactose (the main sugar in milk). In fact, only few people have lactose intolerance, and many people could benefit from consuming milk because it has a high calcium content. This is an example of why it is important to question dietary recommendations that you see in the media. Instead, you should talk to experts who have the proper training based on scientific evidence, and can see the bigger picture.

POPULATION-LEVEL INTERVENTION

A population-based approach considers intervening at all possible levels of practice. Interventions may be directed at the entire population within a community.

To help increase calcium intake in populations where calcium is not readily available, calcium can be included in products such as wheat and water. This is called a **population-level intervention**—we try to raise the calcium intake of the *whole* population. Importantly, this intervention is not very expensive and could save many lives worldwide. To develop this intervention, we first work in the laboratory to find the best ways to enrich water with calcium. Then, we do tests to see how much calcium we can add to the water without it making it taste bad. Finally, we add calcium to the water and see how much it improves the calcium intake of a tested population. In populations that normally have a low calcium intake, we know that raising the calcium intake for pregnant women can reduce the occurrence of preeclampsia by half or more. This can significantly reduce deaths of pregnant women around the world.

THE FUTURE OF MATERNAL HEALTHCARE

My hope is that, in the future, more of the medical procedures that are used will be based on evidence. Some procedures that are currently still used have been scientifically proven to be more harmful than beneficial. Cesarean sections are an important example. A cesarean section is a surgery that is done to deliver a baby. In principle, cesarean sections should only be done when natural delivery is not possible or puts the mother or the baby at risk. Unfortunately, cesarean sections are used far more than they should be—not because women prefer them over natural delivery, but because it is easier for the doctors. But performing cesarean sections can have various negative effects

on women, both in their current pregnancy and in future pregnancies, as well as on the children that are delivered that way [5]. In addition, women can feel sad and stressed if they must undergo a procedure they do not want. This example tells us that it is very hard to change the behaviors and routines of medical doctors, even if those changes are supported by clear scientific evidence.

We still have not been as successful as we would like to be in terms of reducing the number of cesarean sections done around the world, but we keep working on it. In addition to talking with doctors, we also educate women to let them know that they have the right to choose a natural delivery despite what their doctors say. I hope that, with time, we can make both doctors and women aware of the scientific knowledge that can greatly improve the healthcare women receive during pregnancy and delivery. For me, the most gratifying thing in life is to know that I have done something for other people and for the community. We can help people in many ways. I chose to do so through medicine, which is a human-centered profession, but you might choose to do it in other ways. In the world of medicine, we definitely need more people who are searching for ways to improve medical care, particularly for populations that currently do not have the financial means to afford private health care.

ACKNOWLEDGMENTS

I wish to thank Noa Segev for conducting the interview which served as the basis for this paper and for co-authoring the paper, and Iris Gat for providing the figures.

ADDITIONAL MATERIALS

1. Dr. Belizán Live Q&A - 2023 Canada Gairdner Awards Announcement (YouTube)
2. Dr. Belizán's Advice for Young Scientists - 2023 Canada Gairdner Awards Announcement (YouTube)

REFERENCES

1. Bhide, A., Shah, P. S., and Acharya, G. 2018. A simplified guide to randomized controlled trials. *Acta Obstetr. Gynecol. Scand.* 97:380–7. doi: 10.1111/aogs.13309
2. Davey, D. A., and MacGillivray, I. 1988. The classification and definition of the hypertensive disorders of pregnancy. *Am. J. Obstetr. Gynecol.* 158:892–8. doi: 10.1016/0002-9378(88)90090-7
3. Cormick, G., and Belizán, J. M. 2019. Calcium intake and health. *Nutrients* 11:1606. doi: 10.3390/nu11071606

4. Belizán, J. M., Villar, J., Gonzalez, L., Campodonico, L., and Bergel, E. 1991. Calcium supplementation to prevent hypertensive disorders of pregnancy. *N. Engl. J. Med.* 325:1399–405. doi: 10.1056/NEJM199111143252002
5. Belizán, J. M., Althabe, F., and Cafferata, M. L. 2007. Health consequences of the increasing caesarean section rates. *Epidemiology* 18:485–6. doi: 10.1097/EDE.0b013e318068646a

SUBMITTED: 28 May 2023; **ACCEPTED:** 03 August 2023;
PUBLISHED ONLINE: 17 October 2023.

EDITOR: Pasquale Maffia, University of Glasgow, United Kingdom

SCIENCE MENTORS: Melissa Hawkins and Luciana Schleder Goncalves

CITATION: Belizán J (2023) Improving Healthcare for Pregnant Women. Front. Young Minds 11:1230167. doi: 10.3389/frym.2023.1230167

CONFLICT OF INTEREST: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

KIYAN, AGE: 14
I enjoy learning and playing sports, especially football. I also like to cook with my family, especially.

VALENTINA, AGE: 15
I joined the "Health in the Media" Group which is a community project from the Nursing Department at the Federal University of Paraná, Brazil. I am a bilingual (Portuguese and English) 15 year old girl, a high school student, and although I am highly influenced by my mother (a professor and researcher at the University). I love medical TV series, science fiction movies, astronomy and reading novels and fanfics.

AUTHORS

JOSÉ BELIZÁN

José Belizán is an obstetrician. He currently works as principal investigator in the Department of Research in Maternal and Child Health of the Institute for Clinical Effectiveness and Health Policy in Argentina and Researcher at the School of Medicine in the University of Rosario, Argentina, as well as holding roles at other affiliations. He was founder and director of the Rosario Center for Perinatal Studies (CREP) and director of the Latin American Center for Perinatology and Human Development (CLAP) (PAHO/WHO) in Montevideo, Uruguay. He directed the Fogarty Center of the USA National Health Institute in Argentina. In his career he combined both clinical care of pregnant women and conducting research to improve the care of pregnant women and their children. Much of his research resulted in recommendations from the World Health Organization and was adopted by health care providers worldwide. He received several awards in recognition of his contribution to mother and child health, and was active in teaching, and training researchers. *belizanj@gmail.com

HUMAN HEALTH
Published: 17 October 2023
doi: 10.3389/frym.2023.1230790

CAN WE DIAGNOSE BRAIN TUMORS USING A BLOOD TEST?

Gelareh Zadeh [1,2,3*]

[1] *MacFeeters-Hamilton Centre for Neuro-Oncology Research, Princess Margaret Cancer Centre, Toronto, ON, Canada*
[2] *Division of Neurosurgery, Department of Surgery, University of Toronto, Toronto, ON, Canada*
[3] *Krembil Brain Institute, University Health Network, Toronto, ON, Canada*

YOUNG REVIEWERS:

CALEB
AGE: 8

COURTNEY
AGE: 14

SHERESE
AGE: 14

TANVI RAO
AGE: 13

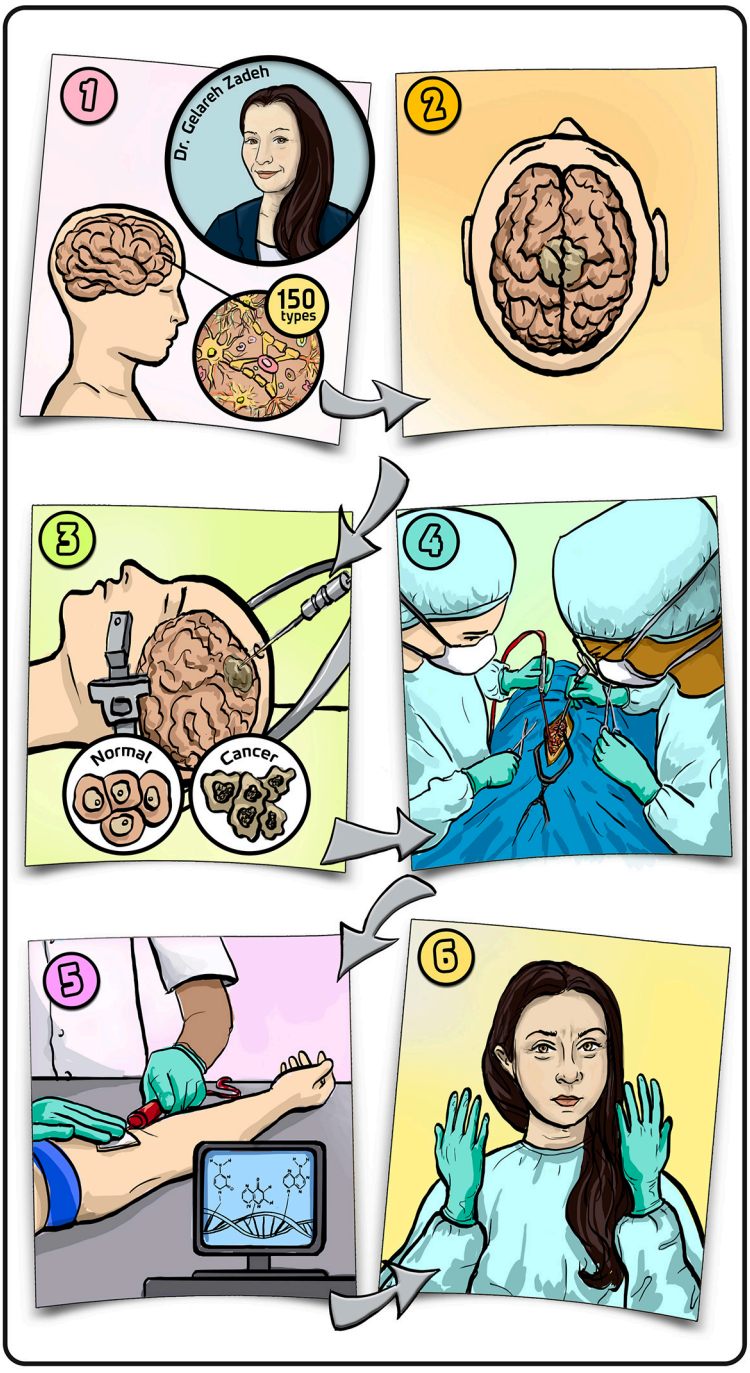
Brain tumors are abnormal growths of cells in the brain, and they can be cancerous or non-cancerous. My job as a neurosurgeon is to perform surgeries to remove harmful brain tumors from patients' brains. Along with this work, I am also a professor at the University of Toronto, where I study brain tumors. By learning more about brain tumors in the lab, I hope to help develop new treatments and diagnostic tools that can improve the ways patients are treated and the outcomes of those treatments. In this article, I will tell you about brain tumors, how they are usually diagnosed and treated, and the next steps we are hoping to take to improve the field of neurosurgery.

Dr. Gelareh Zadeh won the 2023 Canada Gairdner Momentum Award for advancing our understanding of brain tumors at the molecular level. Her research is leading to better ways of identifying, classifying, and managing different types of

brain tumor. This has the potential to improve the medical care that doctors provide to patients suffering from brain tumors.

Graphical Abstract

(1) There are more than 150 types of brain tumors, defined by the types of cells they arise from and whether they are cancerous or not. **(2)** A tumor in the brain looks like a lump of cells that have grown abnormally. **(3)** To determine whether a tumor is cancerous, patients undergo a biopsy in which part of the tissue is surgically removed and analyzed in the lab. **(4)** If the tumor is cancerous, patients have surgery to remove as much of the tumor as possible. **(5)** We hope to replace biopsies with blood tests that can diagnose the type of tumor each patient has. **(6)** What I love about being a neurosurgeon is how my brain gets into full concentration mode from the second I put on my gloves. Illustration by: Iris Gat.



Graphical Abstract

WHAT ARE BRAIN TUMORS?

The brain is a very valuable organ. In many ways, the brain makes us who we are, with our unique personalities and behaviors. The brain is

also very sensitive, and its functioning can be altered by several factors. Brain tumors, which are abnormal growths of cells in the brain, are one of the things that can alter brain functioning. There are over 150 different types of brain tumors [1]. The brain is made of many types of cells, and brain tumors can come from any of these cell types. Some brain tumors are **benign**, meaning that they are not cancerous and do not spread inside the brain. Benign brain tumors are typically cells that have grown out of the normal pattern and, as a result, they put pressure on the brain area where they grow. Some tumors are **malignant** (cancerous) and they can grow and spread rapidly in the brain.

BENIGN

Non-cancerous tumors that do not spread to other parts of the body.

MALIGNANT

Cancerous tumors that can spread to other parts of the body.

NEUROSURGEON

A surgeon that specializes in surgeries on the nervous system, especially the brain and spinal cord.

Most **neurosurgeon**, myself included, usually manage and deal with only about eight to ten common types of brain tumors on a regular basis. Some of the most common brain tumors are glioblastomas and gliomas, which are aggressive cancerous growths; meningiomas, which are generally benign tumors that form from the covering of the brain; and pituitary tumors, which are non-cancerous and form from cells of the pituitary gland, but can compress the nerves connecting the eyes to the brain and cause vision problems. The most challenging tumors to handle are generally those that are wrapped around nerves or blood vessels. In trying to remove such tumors, neurosurgeons can potentially harm the functioning of the nerves or create bleeding in the brain by wounding the blood vessels. These tumors require extremely delicate removal with the use of a surgical microscope. Tumors that are not wrapped around nerves or blood vessels can usually be successfully removed by surgery.

HOW ARE BRAIN TUMORS DIAGNOSED AND TREATED?

Patients with brain tumors usually arrive at the hospital experiencing problems with some brain function (Figure 1A), such as a problem

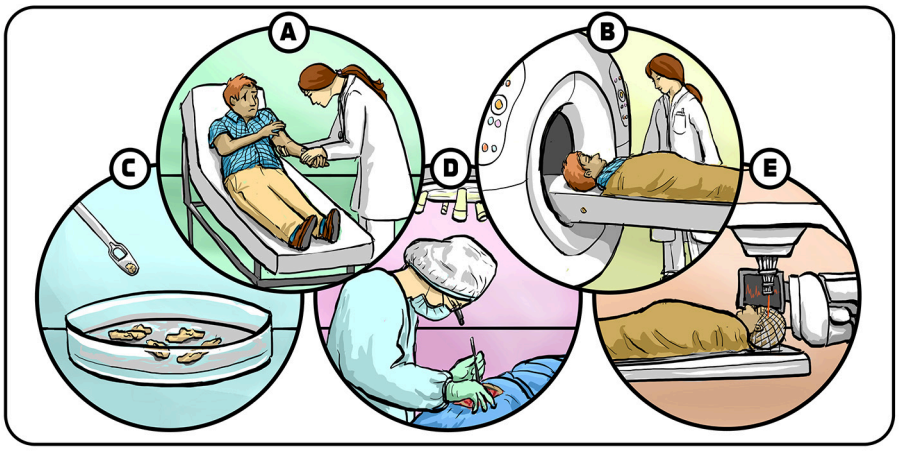


Figure 1

Figure 1

Diagnosis and treatment of brain tumors. **(A)** Patients with brain tumors often arrive in the hospital complaining about a brain-related problem, such as trouble moving their arms or legs. **(B)** Patients are sent for a brain scan and **(C)** a biopsy, to identify whether they have a tumor and they type of tumor. **(D)** If the tumor is cancerous, it is often removed by surgery, followed by **(E)** radiation treatments and chemotherapy, which target the parts of the tumor that could not be removed by surgery. Illustration by: Iris Gat.

with eyesight or hearing, memory, or movement of the limbs; or they might be having seizures. Doctors normally do brain scans on these patients. A common scan is called a computed tomography (CT) scan, which is based on X-rays. If the CT scan finds something suspicious, doctors can also do a more detailed scan using a technique called magnetic resonance imaging (MRI) (Figure 1B). Using the MRI scan, neurosurgeons can confirm whether there is a brain tumor and sometimes tell what type it is. To be sure of the diagnosis, patients often have a **biopsy**, in which part of the suspected tumor is surgically removed and analyzed in a pathology lab (Figure 1C).

BIOPSY

A surgical procedure in which part of a suspicious tissue is removed to be inspected in the lab.

In the case of benign tumors that do not involve critical brain structures like nerve cells and blood vessels, the tumors are removed and usually do not come back. In the case of cancer, the situation is more complex. Brain cancers spread into different tissues in the brain and commonly cannot be removed completely. The parts that can be safely removed are removed surgically (Figure 1D), and the rest of the tumor is treated with other therapies, such as **radiation** and **chemotherapy**, to try to shrink or eliminate the remaining tumor (Figure 1E). Despite the best efforts of neurosurgeons and cancer doctors, sometimes brain tumors come back. Currently, about 30% of the patients in my clinic have repeated surgeries. We can do more than one surgery because our modern surgical techniques and technologies are precise, effective, and do not cause a lot of damage to patients' brains, so the recovery process is easier for patients than it used to be. Part of my motivation as a neurosurgeon is to improve the outcomes of surgeries and find treatments that reduce the negative effects of surgery, radiation, and chemotherapy.

RADIATION

A therapy that uses very energetic beams (commonly x-rays) to kill or slow down the growth of cancerous cells.

CHEMOTHERAPY

A therapy that uses strong drugs to harm cancerous cells by disrupting their growth and division processes of cancerous cells.

CAN WE USE BLOOD TESTS TO DIAGNOSE BRAIN CANCER?

Today, brain cancers are diagnosed using biopsies. Brain biopsies require cutting into the brain, which can be risky and anxiety provoking for the patients, so we would like to find an easier but at the same time reliable way. It may be possible to use blood tests to diagnose brain cancers [2]. These blood tests are based on **biomarkers**, which are biological materials that are present in the blood and that we can measure. Tumors often release biomarkers into the blood by shedding parts of themselves, including their DNA. We can capture and concentrate tumor DNA present in the blood using magnetic methods, and analyze its composition. When we analyze tumor DNA, we are looking for a specific "signature" of molecules containing three hydrogen atoms and one carbon atom. Molecules of this form are called a methyl group, and they get attached to different parts of the DNA. These methyl groups are like markers signaling which genes should be silenced and which genes should be activated. This process of silencing and activating genes using methyl groups is called **DNA methylation** [3]. DNA Methylation is unique to each tissue, so

BIOMARKER

A biological material that can be found in body fluids like blood and is used to diagnose a disease.

DNA METHYLATION

A way in which the body turns genes on and off, by adding or removing chemical groups called methyl groups to the DNA.

it can serve like a specific "fingerprint" of that tissue. In our case, methylation can serve as a fingerprint for each of the 150 types of brain tumors. If we do a blood test and find DNA that has the methylation signature of a certain type of brain tumor (Figure 2), we can in principle know which type of tumor the patient has without having to take a sample of the tumor through a biopsy.

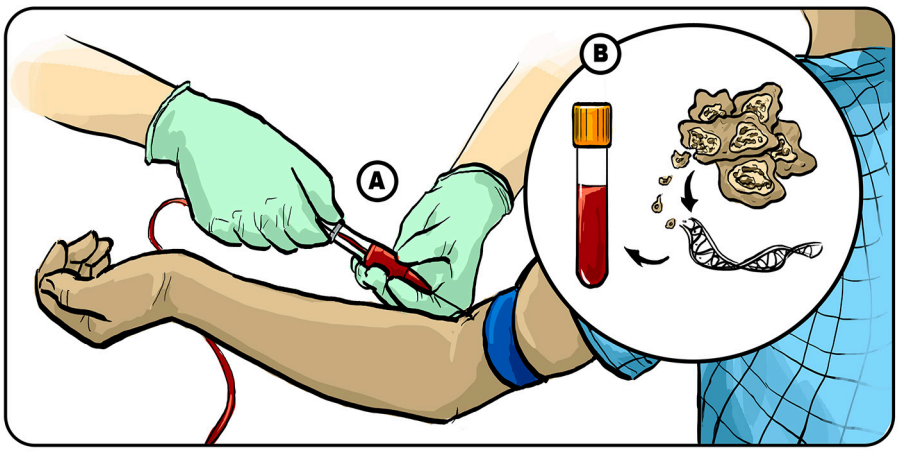


Figure 2

Figure 2

Using blood tests to diagnose brain tumors. **(A)** We are currently working on developing blood tests to diagnose which type of brain tumor a patient is suffering from. **(B)** After we take the patient's blood, we concentrate the DNA biomarker from the tumor and look at the DNA methylation "fingerprint", which can tell us which type of brain tumor the DNA came from. Illustration by: Iris Gat.

Currently, the accuracy of blood tests to diagnose brain cancers is about 80%. Before blood tests can replace biopsies, we must increase the accuracy to at least 90%. In medicine, new treatments must surpass existing treatments before they become the new standard. Even after a new standard is reached, it usually takes a few years until it is widely accepted by doctors around the world. I believe that, in a few years, diagnostic blood tests for brain tumors will replace biopsies. That will revolutionize the way we treat brain tumors—not only because we will no longer need biopsies, but also because blood tests could be a great tool for detecting tumors that return after surgery. Currently, we rely on MRI to see if tumors come back after surgery, but by the time we see the tumor using MRI, the tumor has already grown quite large. Our aim is to have sensitive blood tests for DNA methylation, to diagnose a returning cancer long before it reaches a critical mass of cancerous cells. This could help us treat returning cancers early, which could save lives. Additionally, when tumors come back, they often have a different composition of cells, depending on which cells survived previous treatments. In other words, the cells that survived may have a different genetic mix than the original tumor. This means that the second treatment might need to be different than the first—and knowing the exact composition of the returning tumor based on its methylation signature could help us design the best treatment.

THE FUTURE OF BRAIN CANCER THERAPY

Over the last few decades, our ability to identify tumors based on DNA biomarkers has significantly increased. Now we know that specific methylation signatures are associated with specific tumors, which tells us that there are many subtypes of the types of brain tumors we previously identified. Tumors that look identical under the microscope may be classified differently based on their genetic mutations, and the precision with which we are able to recognize these tumors using blood samples is increasing. The next step is to develop specific treatments for each type of tumor.

We recently published a study in which we used DNA differences to predict how effective a treatment would be for a brain tumor called glioblastoma [4]. We injected a virus called adenovirus into the glioblastoma tumor. When the virus enters cancerous cells, it replicates inside the cells and the cells burst. This burst triggers the immune system to attack cancerous cells. We also gave the patients medicines to boost their immune systems. We looked both at the tumors and at the immune cells to see if there was a genetic signature that could tell us which patients would respond well to this treatment and which would not. We found that, if certain genes of the immune system were highly activated, then patients were likely to respond to the treatment. If the genes were minimally activated, it was not likely that the patient would respond well to the treatment. This is an important demonstration of our ability to use genetic signatures to "tailor" treatments to specific patients. We hope that future studies like this one will help us to understand which treatments our patients should respond to. We also want to develop *more* treatments for brain tumors.

I have dedicated my life to both researching how to improve diagnosis and treatments for brain tumors, and to performing brain surgeries on patients. Learning how to balance research and medical practice was a big challenge. Another challenge that I had to face was how to avoid becoming discouraged when complications happen to patients. As a doctor, I naturally want all my surgeries to be perfect—but sometimes things get complicated, and patients are left in challenging situations. This is very tough for any neurosurgeon to experience. I found that talking to with honesty to patients and colleagues about these experiences, while also learning how to manage continuing to take care of the patients is very important and helpful. I also make sure to learn from every experience I have by giving my fullest attention to what I do—be it caring for patients or conducting scientific research.

ADDITIONAL MATERIALS

1. Dr. Gelareh Zadeh-2023 Canada Gairdner Momentum Award.

2. Meet 2023 Gairdner Momentum Award winner Dr. Gelareh Zadeh (YouTube).

ACKNOWLEDGMENTS

I wish to thank Noa Segev for conducting the interview which served as the basis for this paper and for co-authoring the paper, and Iris Gat for providing the figures.

REFERENCES

1. Kleihues, P., Louis, D. N., Scheithauer, B. W., Rorke, L. B., Reifenberger, G., Burger, P. C., et al. 2002. The WHO classification of tumors of the nervous system. *J. Neuropathol. Exper. Neurol.* 61, 215–225. doi: 10.1093/jnen/61.3.215
2. Nassiri, F., Chakravarthy, A., Feng, S., Shen, S. Y., Nejad, R., Zuccato, J. A., et al. 2020. Detection and discrimination of intracranial tumors using plasma cell-free DNA methylomes. *Nat. Med.* 26, 1044–1047. doi: 10.1038/s41591-020-0932-2
3. Moore, L. D., Le, T., and Fan, G. 2013. DNA methylation and its basic function. *Neuropsychopharmacology* 38, 23–38. doi: 10.1038/npp.2012.112
4. Nassiri, F., Patil, V., Yefet, L. S., Singh, O., Liu, J., Dang, R. M., et al. 2023. Oncolytic DNX-2401 virotherapy plus pembrolizumab in recurrent glioblastoma: a phase 1/2 trial. *Nat. Med.* 29, 1370–1378. doi: 10.1038/s41591-023-02347-y

SUBMITTED: 29 May 2023; **ACCEPTED:** 30 August 2023;
PUBLISHED ONLINE: 17 October 2023.

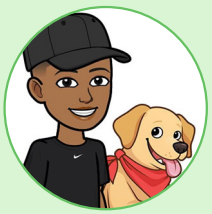
EDITOR: Fulvio D'Acquisto, University of Roehampton London, United Kingdom

SCIENCE MENTORS: Kathleen Carol Bubb and Mitali Singh

CITATION: Zadeh G (2023) Can We Diagnose Brain Tumors Using a Blood Test? Front. Young Minds 11:1230790. doi: 10.3389/frym.2023.1230790

CONFLICT OF INTEREST: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS



CALEB, AGE: 8

Caleb is an 8 year old future marine biologist who is fascinated by the differences in all classes of animals and how human beings can learn from and impact on our environment. He draws, writes short stories and keeps his CPR skills up to date for fun. He loves conducting experiments at home, swimming and is a video game enthusiast. On top of that he is an avid hiker and enjoys interacting with animals in their natural environment.

COURTNEY, AGE: 14

Courtney is 14 and dreams of becoming a graphic designer. Until then she immerses herself in everything art, dance, music, and science too.

SHERESE, AGE: 14

Sherese is a 14-year-old gifted artist, dancer, and writer who enjoys science and building things. She not set on a career as yet but enjoys using dance to create and share positive stories to the world. She speaks Mandarin and has a passion for learning everything about everything.

TANVI RAO, AGE: 13

Meet Tanvi Rao, a 13-year-old with keen interest in both science and art. She is a science enthusiast, devouring knowledge about advancements in her favorite subject. Additionally, Tanvi is also an art lover, creating masterpieces with her boundless creativity. Tanvi is always up for learning anything new related to science.

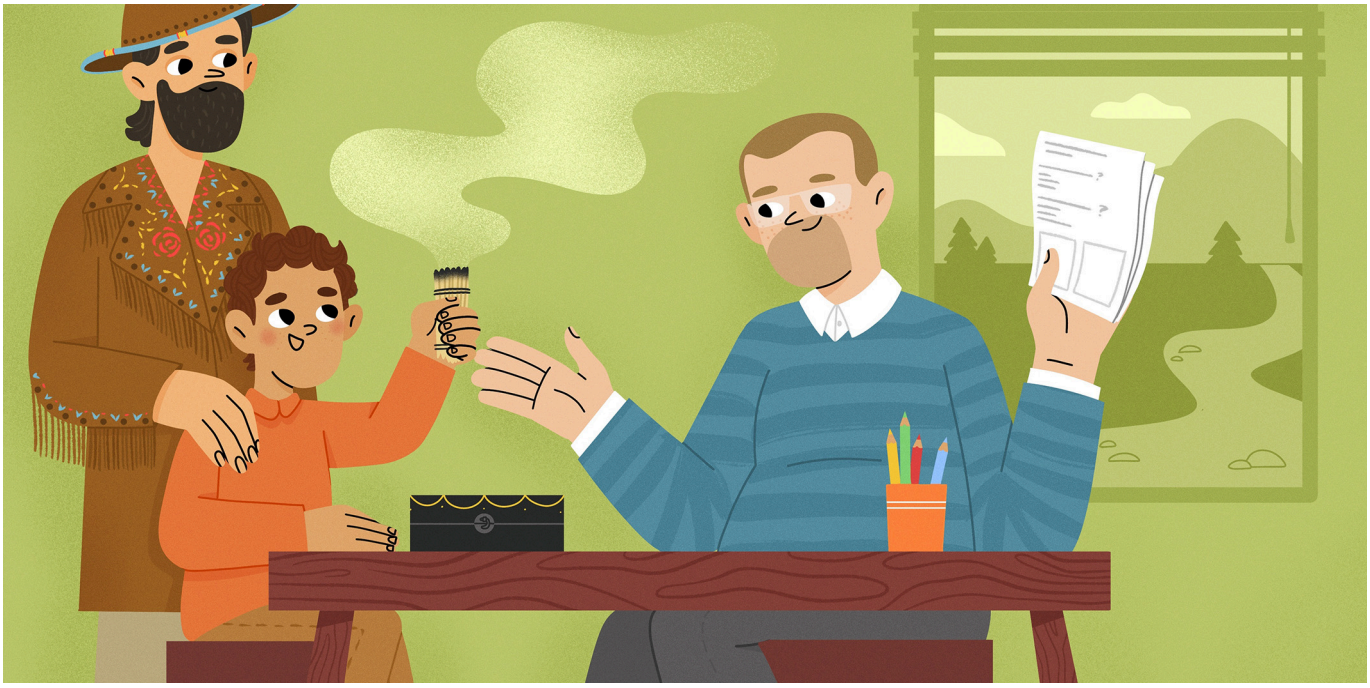
AUTHORS

GELAREH ZADEH

Dr. Gelareh Zadeh is Co-Director of the Krembil Brain Institute, a Senior Scientist at the Princess Margaret Cancer Centre and Head of the Division of Neurosurgery at the University Health Network. She is also Professor of Neurosurgery at the University of Toronto. Dr. Zadeh was born in Iran and moved to Canada as a teenager. She splits her time between clinical work and academic research. At the clinic, Dr. Zadeh is caring for patients with brain tumors and performing surgeries to remove harmful tumors. In her lab, Dr. Zadeh works with her students to search for new and improved ways to identify brain tumors, and study how they respond to different therapies. In recent years, Dr. Zadeh and her colleagues have been developing a promising method for diagnosing brain tumors using a blood test, which could replace invasive surgical procedures that are currently used to diagnose brain tumors. Dr. Zadeh has two children and in her (little) spare time she likes to spend time with family and travel.
*kids@frontiersin.org

frontiers | Frontiers for Young Minds

NEUROSCIENCE AND PSYCHOLOGY
Published: 17 October 2023
doi: 10.3389/frym.2023.1236682



IMPROVING MENTAL HEALTH WITHIN INDIGENOUS COMMUNITIES

Christopher Mushquash *

Department of Psychology, Lakehead University, Thunder Bay, ON, Canada

YOUNG REVIEWERS:

HENRY
AGE: 15

NORAH
AGE: 10

In many places in the world, there are communities of Indigenous Peoples—the first Peoples that inhabited those lands. Each community has its own unique history, culture, practices, spiritual beliefs, and worldviews. I work as a psychologist in Indigenous Peoples' communities in northern Canada, exploring how we can use scientific methods, combined with the traditional wisdom of communities and culture, to improve mental health. In this article, I will tell you about Indigenous Peoples, how many view health and wellness, and what I do to support their mental health—specifically with groups of young people who are having trouble with substance use. I hope that this article will inspire you to find ways to combine scientific approaches with traditional wisdom, to improve your own wellbeing.

Dr. Christopher Mushquash won the 2023 Canada Gairdner Momentum Award for mental health and substance use research performed in close collaboration with Indigenous communities. This research is assisting the development of

services for Indigenous children, adolescents, and adults, that suit the culture and context in which they live.

Graphical Abstract

Article Summary. **(1)** My work with Indigenous communities is based on relationships—cooperation, trust, and a shared vision. **(2)** I meet Indigenous Peoples in my clinic and try to deeply understand their experiences. **(3)** The healing practices I offer my patients combine ancient wisdom (such as traditional ceremonies) and modern psychology techniques (such as questionnaires). **(4)** In one study, we found that some Indigenous Peoples are having trouble with substance use, because of trauma. **(5)** Understanding the source of their challenges empowers young people to heal and learn positive coping behaviors. **(6)** I encourage youth to: know who you are and where you came from, and lean on the things that bring you strength. Illustration by: Iris Gat.

Graphical Abstract

WHO ARE INDIGENOUS PEOPLES?

Do you know who lived on the land you live on 1,000 years ago? Or 5,000 years ago? There are three broad groups of Peoples that have been living in Canada (where I live), for thousands of years. These groups are called First Nations, which is the group I come from (Figure 1A); Inuit, who are the original inhabitants of the northernmost parts of Canada (Figure 1B); and Métis, who have a distinct culture with combined ancestry of both First Nations Peoples and European settlers (Figure 1C). Collectively, these groups are called **Indigenous Peoples**. According to the government of Canada, Indigenous Peoples is "a collective name for the original Peoples of North America and their descendants." In other words, Indigenous Peoples are considered the first people who inhabited the lands that make up many of the countries that exist today. In Canada, there are Indigenous Peoples who live in urban centers and there are Indigenous Peoples who live in smaller, rural communities. Some Indigenous Peoples live in remote communities that are only accessible by airplane, or accessible by roadway only in the winter when the lakes are frozen!

INDIGENOUS PEOPLES

The original inhabitants of an area.

Figure 1

Indigenous Peoples in Canada. In Canada, there are three main groups of Indigenous Peoples: **(A)** First Nations, **(B)** Inuit, and **(C)** Métis. Illustration by: Iris Gat.

Indigenous Peoples have very distinct histories, cultures, languages, practices, spiritual beliefs, and worldviews. What is shared between *all* the Indigenous Peoples in Canada is a history of **colonization**, in which people from Europe came to settle in Canada. As part of colonization, a lot of the traditional cultural practices of Indigenous Peoples were disrupted. Some cultural practices were made illegal, and people were physically threatened or harmed for engaging in them. This contributed to some of the mental and emotional health difficulties that Indigenous Peoples in Canada are now experiencing [1]. A big part of my work is to become familiar with Indigenous Peoples' stories, cultures, and practices, and to find new ways to contribute to their mental health.

COLONIZATION

An act in which settlers seek control over the Indigenous Peoples of an area and the lands they inhabit.

WHOLISTIC MENTAL HEALTH

Many non-Indigenous communities in Canada often think about health functionally, as simply being free from any type of physical illness. In contrast, for many Indigenous Peoples, health is understood in the context of being well, or having a sense of wellbeing in all aspects of human experience. Many Indigenous Peoples, including myself, view health and wellbeing as keeping a balance between the mental, emotional, physical, and spiritual areas of our lives. We also include social and environmental factors as part of health. In other words, we believe that people's health is also determined by life circumstances, including education and income, whether they can regularly access enough healthy food and clean water to drink, what kinds of spaces they live in and whether their housing is enough for them and the other people they live with, and whether their physical environments are polluted. These are broad understandings of health, which Indigenous Peoples have held for hundreds to thousands of years, and these understandings are now spreading to non-Indigenous communities—and I am glad for it.

CULTURE-BASED APPROACHES

These are techniques that are rooted in the cultural wisdom of the community that the psychologist is working with.

The focus of my work is mental health. I try to understand how we can use **culture-based approaches**—approaches that honor the cultural wisdom, knowledge, and practices—to help address current mental health and substance use difficulties faced by some Indigenous Peoples [2]. A big part of my work is to try to understand how to combine my knowledge and training in psychology with traditional practices and customs, to best benefit the health of Indigenous Peoples and communities. To do so, I must understand the bigger context of how each community views health in general, and mental health in particular, and I must be familiar with the common practices and ceremonies held in that community. This knowledge, along with a close relationship with the Indigenous community, helps me to come up with new ways of harmoniously weaving contemporary approaches and practices into the practices traditionally used by that community, to give people more tools with which to address their mental health difficulties.

HOW I WORK WITH INDIGENOUS PEOPLES

When I conduct a new study with Indigenous Peoples, I work very closely to understand their values. This helps me to develop trust and make sure that our goals are aligned. I then take the shared wisdom from both modern psychology *and* Indigenous culture-based methods, and collaborate with partners from community to generate research questions for mental health studies, such as how can we help young Indigenous Peoples in your community to regulate their emotions? Finally, I use my findings to improve wellness, to promote the use of certain practices and treatments, or to demonstrate how things might work differently and why that might be the case.

I am fortunate to work in a psychology clinic that is part of a community-based organization. This means that I work with the local community, and I learn about peoples' needs, priorities, and experiences. I do my best to understand people as deeply as I can and shed light on their experiences based on my clinical training and knowledge. Often, direct exposure to people's experiences helps me to get a general idea of the common difficulties that many people in that community are experiencing. Then I can use current, science-based psychology tools to offer a new service that could help people while also respecting their cultural beliefs and practices. Finally, I evaluate how effective the services are, for example by asking the people to fill out questionnaires (some of which we have developed in collaboration with people from the community!) report on whether the new treatment helped them to deal with their difficulties [3]. I also collect data using sharing circles, where I hear stories that people communicate about their experiences and the meaning a specific treatment has for them.

HELPING YOUNG PEOPLE DEAL WITH SUBSTANCE USE DIFFICULTIES

SUBSTANCE USE

The use of substances, such as drugs, tobacco, or alcohol, that could have negative effects on the person and/or the people around them.

ADVERSE CHILDHOOD EXPERIENCES

Difficult experiences that people had in childhood, that might have effects on health and wellness in adult life.

INTERGENERATIONAL TRAUMA

Emotional challenges, or traumatic experiences, that are passed between generations—through families.

My colleagues, students, and I are working on a study with First Nations Peoples who are having trouble with **substance use** [2]. We wanted to understand the role of **adverse childhood experiences**, which are difficult, sometimes traumatic experiences that people have in childhood. Scientists have studied adverse childhood experiences since the 1990s, but this type of work has not typically been done in close collaboration with First Nations Peoples. So, our close relationships and collaboration with the First Nations community is unique and significant.

In this study, we also wanted to understand the effects of colonization and **intergenerational trauma** on the experiences of young children (Figure 2). Intergenerational trauma is trauma that has been passed down through the generations. When European settlers came to Canada and cultural practices of Indigenous Peoples became disrupted, it negatively affected mental wellbeing. We found various connections between colonization, intergenerational trauma, and the disruption of relationships between children and parents. When early attachment is disrupted through colonial processes, children's abilities to regulate their emotions and control their impulses can also disrupted. This can lead to an increase in the risk that an individual experiencing emotional challenges might use substances to manage those difficult feelings. We also found that the difficulties First Nations Peoples experienced through childhood were, on average, larger than the difficulties experienced by non-Indigenous Peoples, due to the intergenerational trauma that resulted from colonization. Finally, we found that, unfortunately, such difficult experiences are increasing in some First Nations communities.

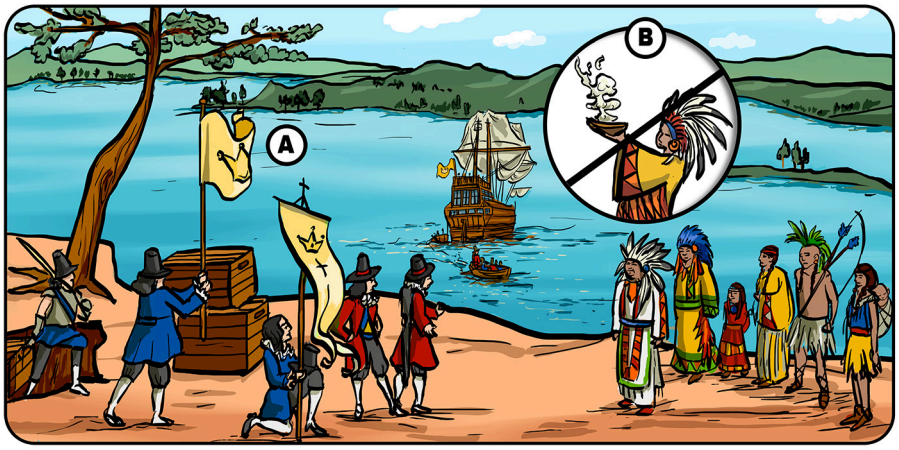


Figure 2

Figure 2

Intergenerational trauma and substance use. Substance use problems in young Indigenous Peoples can be rooted in intergenerational trauma. This trauma interferes with emotional development in childhood, making it more difficult to manage difficult feelings in adolescence. **(A)** Much of this trauma resulted from colonization. **(B)** The traditional cultural practices of Indigenous Peoples were disrupted, and in some cases outlawed, which continues to have negative impacts on the wellbeing of the community for generations. Illustration by: Iris Gat.

To support young Indigenous Peoples in dealing with substance use, we developed ideas from psychology to include specific difficulties experienced by First Nations Peoples. Then we worked with the First Nations Peoples who experienced these difficulties to develop new understandings about how to cope with trauma and the challenging emotions they might experience. This kind of understanding gives Individuals the power to develop new skills that can have positive effects on their health. We also help people to learn about how emotional injuries from past trauma can be healed by cultural practices. For example, people who are trying to regulate their emotions and deal with difficult past experiences might be helped by participating in cultural and spiritual practices like sweat lodges or smudge ceremonies. These traditional practices can help people to process what they have experienced and help them to focus on the current moment—which can help them to regulate their emotions and lead to new ways to manage strong feelings in difficult moments.

I am happy to say that I am hopeful about the future. I think that there is more national and international attention on Indigenous Peoples' mental health and wellness today than there has ever been before. Many people in our communities are working to improve the mental health of Indigenous Peoples, including Elders, cultural teachers, community members, health professionals and researchers; and many young people who are joining these professions have a lot to contribute. My vision for the future is that the next generations of young scientists and clinicians (like you!) will be confident in their ability to help answer questions that are important to Indigenous Peoples. This career is very meaningful to me, and I believe many young Peoples will find it incredibly meaningful as well. Whichever route you choose along your life's path, remember who you are and where you came from, and lean on the things from your own unique background and experience that bring you strength.

ADDITIONAL MATERIALS

1. Dr. Christopher Mushquash—2023 Canada Gairdner Momentum Award.
2. 2023 Canada Gairdner Momentum Award Laureate: Dr. Christopher Mushquash (YouTube).
3. Dr. Mushquash Live Q&A-2023 Canada Gairdner Awards—Advice for Young Scientists.

ACKNOWLEDGMENTS

I wish to thank Noa Segev for conducting the interview which served as the basis for this paper and for co-authoring the paper, and Iris Gat for providing the figures.

REFERENCES

1. Nelson, S. E., and Wilson, K. 2017. The mental health of Indigenous Peoples in Canada: a critical review of research. *Soc. Sci. Med.* 176:93–112. doi: 10.1016/j.socscimed.2017.01.021
2. Rowan, M., Poole, N., Shea, B., Gone, J. P., Mykota, D., Farag, M., et al. 2014. Cultural interventions to treat addictions in Indigenous populations: findings from a scoping study. *Subst. Abuse. Treat. Prev. Policy*. 9:1–27. doi: 10.1186/1747-597X-9-34
3. Fiedeldey-Van Dijk, C., Rowan, M., Dell, C., Mushquash, C., Hopkins, C., Fornssler, B., et al. 2017. Honoring Indigenous culture-as-intervention: development and validity of the Native Wellness Assessment™. *J. Ethn. Subst. Abuse* 16:181–218. doi: 10.1080/15332640.2015.1119774

SUBMITTED: 08 June 2023; **ACCEPTED:** 04 September 2023;
PUBLISHED ONLINE: 17 October 2023.

EDITOR: Pasquale Maffia, University of Glasgow, United Kingdom

SCIENCE MENTORS: Pranoot Tanpaiboon and Alexandra V. Ulyanova

CITATION: Mushquash C (2023) Improving Mental Health Within Indigenous Communities. Front. Young Minds 11:1236682. doi: 10.3389/frym.2023.1236682

CONFLICT OF INTEREST: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

HENRY, AGE: 15

My name is Henry, and I am a student at the Harrow School in the U.K. I am planning to be a doctor and am currently studying Biology, Chemistry, Philosophy, and Russian at the A-Level.

NORAH, AGE: 10

My name is Norah. I am 10 years old. I like to experiment with expired things (shampoo, lotion, baby powder, toothpaste etc.) to see if I can create anything useful (which never happens). I also like to bike in my spare time. My favorite subjects in school are History and Science. One of my biggest goals are to learn five languages and earn a black belt in the style of karate that I learn.

AUTHORS

CHRISTOPHER MUSHQUASH

Dr. Christopher Mushquash, HBSc., M.A., Ph.D., C.Psych., is Anishinawbe (Ojibway), and a member of Pawgwasheeng (Pays Plat First Nation). He is a Professor in the Department of Psychology at Lakehead University, and the Northern Ontario School of Medicine University, Clinical Psychologist at Dilico Anishinabek Family Care, Vice President Research at the Thunder Bay Regional Health Sciences Centre, and Chief Scientist at the Thunder Bay Regional Health Research Institute. He is also Director of the Centre for Rural and Northern Health Research at Lakehead University. Dr. Mushquash is a Canada Research Chair in Indigenous Mental Health and Addiction, with expertise in rural and northern clinical practice and the development of culturally appropriate interventions for mental health and addiction difficulties in First Nations children, adolescents, and adults. He is a researcher, clinician, and First Nation scholar who was born and raised in rural Northwestern Ontario. *chris.mushquash@lakeheadu.ca

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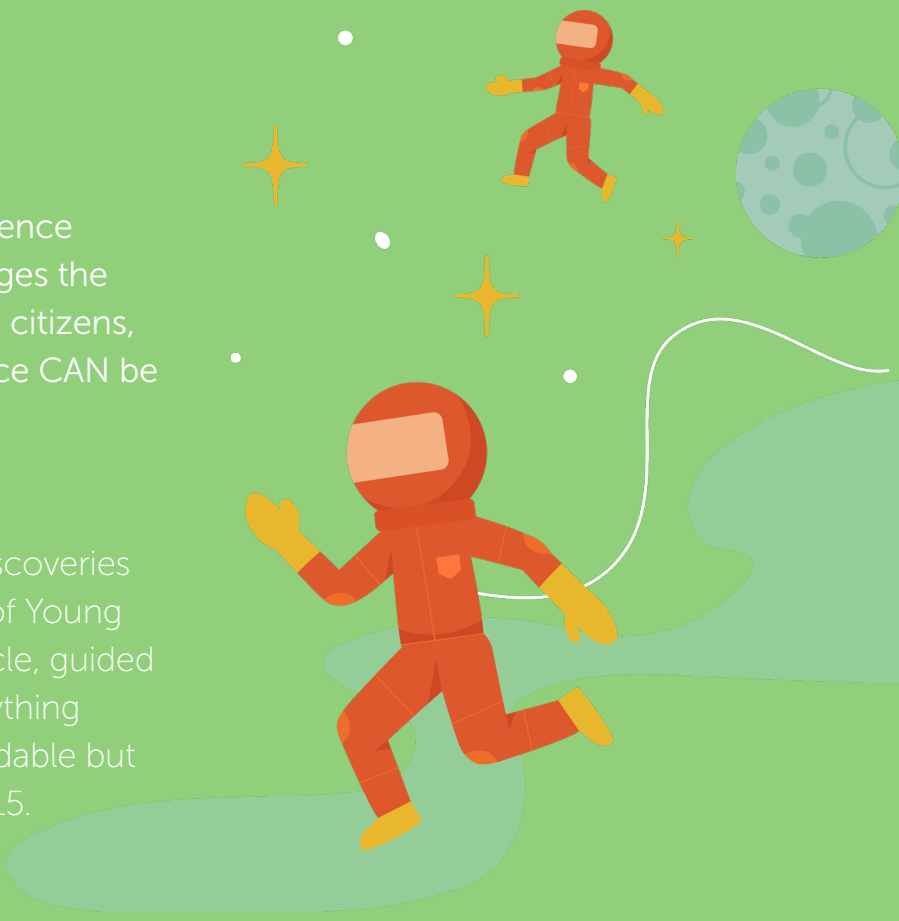

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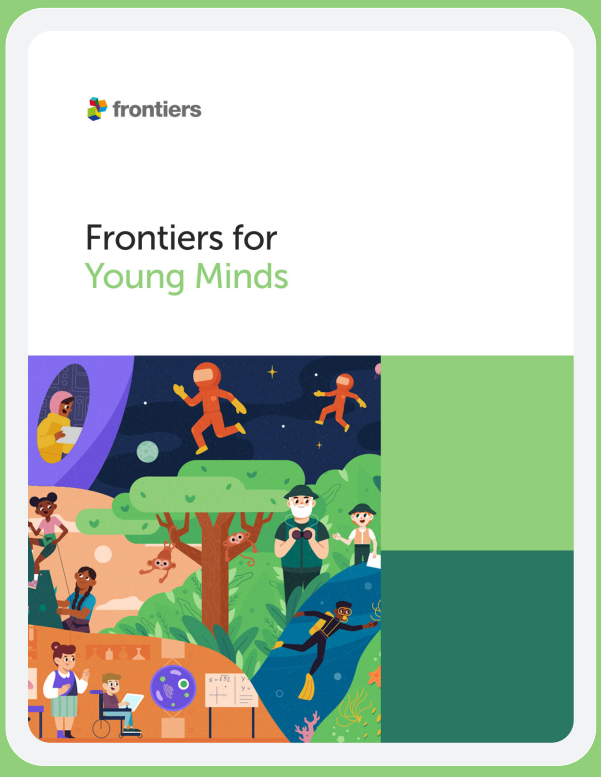

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