

2026 CANADA GAIRDNER AWARD WINNERS

Explore the science behind today's biggest
breakthroughs



TABLE OF CONTENTS

About the Gairdner Foundation	3
Meet the 2026 Gairdner Award Winners	4
About Gairdner Connects	6
About this Collection	7

GAIRDNER LAUREATE ARTICLES

Karen Maxwell	8
<i>Bacteria vs bacteria-attacking viruses: The fight against antibiotic resistance</i>	
Aaron Phillips	15
<i>A shock to the system: Restoring blood pressure function after spinal cord injury</i>	
Jeffery W. Kelly	22
<i>Preventing Protein Misfolding: The Battle Against Toxic Protein Clumps</i>	
John R. Yates III, Ruedi Aebersold, and Matthias Mann	28
<i>Proteomics: How we know what we know about proteins</i>	
Wolfgang Baumeister	38
<i>Zooming in on biological molecules: A new perspective</i>	
John D. Clemens and Jan Holmgren	45
<i>From discovery to distribution: Bringing the oral cholera vaccine to the world</i>	

ABOUT GAIRDNER

The mission of the Gairdner Foundation is to celebrate, inform and inspire scientific excellence around the globe.

Established in 1957, the Gairdner Foundation 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 the prestigious annual Canada Gairdner Awards, the Foundation celebrates the world's most creative and accomplished researchers whose work is improving the health and wellbeing of people around the world. **The Canada Gairdner Awards are recognized internationally as being among the most prestigious in the world, based on our reputation for rigorous review and early recognition of breakthroughs in science.**

The Gairdner Foundation brings people together to openly discuss science in order to better engage the public, understand the problems we face, and work together to find solutions. Through Gairdner Connects, our national outreach program, we bring science to communities across Canada to inspire future innovators and spark public dialogue about the role of research in addressing the world's most pressing health challenges.

BY THE NUMBERS

5 CANADA GAIRDNER
International Awards
For excellence in biomedical research

2 PETER GILGAN CANADA GAIRDNER
Momentum Awards
For mid-career investigators with exceptional research

1 JOHN DIRKS CANADA GAIRDNER
Global Health Award
For outstanding achievements in global health research

443 AWARDS to scientists from over **40** countries

103
Gairdner awardees have gone on to win the **Nobel Prize**



20 CANADIAN UNIVERSITIES | ENGAGING **6000+** students and researchers annually through outreach programs that give Canadians access to world-renowned scientists



MEET THE 2026 AWARD WINNERS

CANADA GAIRDNER INTERNATIONAL AWARD

Awarded for establishing the foundations of modern systems proteomics through transformative innovations in quantitative protein measurement, mass spectrometry technologies, and computational analysis.



John R. Yates III

John Lytton Young Endowed Chair and Professor,
Department of Integrative Structural and Computational
Biology, Scripps Research, La Jolla, United States



Ruedi Aebersold

Professor Emeritus, Molecular
Systems Biology, Institute of
Molecular Systems Biology,
Department of Biology, ETH Zurich,
Switzerland



Matthias Mann

Director of Department of Proteomics
and Signal Transduction, Max Planck
Institute of Biochemistry, Martinsried,
Germany



Awarded for developing cryo-electron tomography, a method that visualizes molecular structures inside intact cells at near-native resolution, creating a new way to study cellular architecture and revealing the inner workings of life at the molecular level.



Wolfgang Baumeister

Director Emeritus and Scientific Member, Max-Planck-Institute of
Biochemistry, Martinsried, Germany; Distinguished Professor, ShanghaiTech
University, China

Awarded for discovering the anti-aggregation drug, tafamidis, the first effective treatment for a human amyloid disease, specifically transthyretin amyloidosis, providing the first pharmacological evidence that protein aggregation drives neurodegeneration.



Jeffery W. Kelly

H. Lutcher Brown Professor of Chemistry, Department of Chemistry, Scripps
Research, La Jolla, United States

MEET THE 2026 AWARD WINNERS

JOHN DIRKS CANADA GAIRDNER GLOBAL HEALTH AWARD

Awarded for advances in understanding cholera disease and immunity, and for the development and evaluation of safe, effective, and affordable inactivated oral cholera vaccines that have enabled cholera control worldwide.



John D. Clemens

Senior Scientific Advisor to the Director General, International Vaccine Institute, Seoul, South Korea; Adjunct Professor of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, United States



Jan Holmgren

Senior Professor, Sahlgrenska Academy, University of Gothenburg, Sweden



PETER GILGAN CANADA GAIRDNER MOMENTUM AWARD

Awarded for uncovering the molecular strategies bacteria use to defend against viruses, revealing how viruses known as bacteriophages evade these defences, and laying the foundation for next-generation precision phage therapies to combat antibiotic-resistant infections.



Karen Maxwell

Professor, Department of Biochemistry, Temerty Faculty of Medicine, University of Toronto, Canada

Awarded for pioneering work that restores blood pressure control after spinal cord injury, reducing life-threatening complications, improving daily functioning, and transforming clinical care for people living with paralysis.



Aaron Phillips

Associate Professor, Departments of Clinical Neurosciences, Cardiac Sciences, Physiology and Pharmacology, University of Calgary; Associate Dean, Innovation and Commercialization, Cumming School of Medicine, University of Calgary, Canada

GAIRDNER CONNECTS

Gairdner Connects brings award-winning scientists to communities across Canada to engage, inspire, and spark dialogue. In doing so, it fosters meaningful connections between Gairdner Award winners and the next generation of researchers. **Through interactive events, classroom visits, community discussions, and digital resources, we inspire future innovators and spark dialogue about the role of science in addressing global health challenges.**

This booklet, developed in partnership with the **Canadian Association for Girls in Science (CAGIS)**, is part of the Gairdner Foundation's student outreach program to bring science to communities across Canada.

IS THERE A PROGRAM NEAR YOU?

Visit gairdner.org to explore Gairdner Connects, featuring all our student events and digital resources.



gairdner
CONNECTS

ABOUT THIS COLLECTION

This collection introduces the discoveries of the 2026 Canada Gairdner Award winners, among the world's leading biomedical and global health researchers. From the inner workings of our cells to new approaches to preventing disease and improving treatment, these stories explore research shaping the future of human health.

Each article was written by Gairdner student intern **Leanne Cherry**, an undergraduate student at McGill University studying Cognitive Science and Communication Studies, and developed in collaboration with the Award winners themselves. Passionate about science communication, Leanne is interested in making research accessible and combating science and health misinformation.

The articles were also reviewed by the students from the **Canadian Association of Girls in Science (CAGIS)**, whose thoughtful feedback helped make these stories clear, accurate and engaging for young readers.

Illustrations were created by **Heather Ng-Cornish**, an illustrator and communicator based in Ontario. Heather brings her science communication experience to her illustrations, creating clear, colourful and accessible visuals that help bring scientific ideas to life. To see more of her work, visit www.heatherngcornish.com

Inside, you'll discover the science behind this year's award-winning research and explore questions such as:

- How can scientists identify, measure and study thousands of proteins?
- How can we stop misfolded proteins from causing disease?
- How can scientists use 3D images to see inside cells?
- How can oral vaccines help prevent cholera?
- How can viruses help us fight antibiotic-resistant bacteria?
- How can technology help regulate blood pressure after spinal cord injury?

The Gairdner Foundation is committed to sharing the excitement of discovery with people of all ages. We hope this collection sparks your curiosity, encourages you to ask big questions, and inspires you to imagine the discoveries still waiting to be made.



LEANNE
CHERRY



HEATHER
NG-CORNISH



BACTERIA VS BACTERIA- ATTACKING VIRUSES: THE FIGHT AGAINST ANTIBIOTIC RESISTANCE

DR. KAREN MAXWELL

**PETER GILGAN CANADA GAIRDNER MOMENTUM AWARD
WINNER**

Professor, Department of Biochemistry, Temerty Faculty of Medicine,
University of Toronto, Canada

SUMMARY

Karen Maxwell has uncovered crucial details about how bacteria defend themselves against viruses, and how these viruses attack back. Maxwell's research marks a significant step in the field of phage therapy, which would allow us to target antibiotic-resistant bacteria with the help of bacteria-killing viruses, known as phages.

STUDENT REVIEWERS:



ADRIENNE
Grade 12



DEEPA
Grade 12



RANEEM
First year
university



VIENNA
First year
university

Antibiotics are a major lifesaver (literally) when it comes to treating bacterial infections. Before antibiotics, getting a mere paper cut could be a death sentence. However, despite how useful antibiotics have been to us, we have run into a new problem: antibiotic resistance. Because we have relied so heavily on antibiotics, we have given bacteria too many chances to adapt, making them much more difficult to combat. Antibiotic resistance poses a major threat to global health—but what if we could team up with bacteria's worst enemy to manage our antibiotic resistance problem?

Bacteriophages, or simply phages, are a kind of virus that only target and kill bacteria (**Figure 1**). Dr. Karen Maxwell, a researcher and professor in biochemistry at the University of Toronto, has uncovered crucial details about phage-bacteria conflict, exploring how bacteria defend themselves against phages, how phages overcome these defenses, and how both of them keep evolving to try to outsmart one another. Maxwell's work can help us figure out how best to use their interactions to our advantage.



FIGURE 1

A bacteriophage, also known as a phage, is a kind of virus that only target and kill bacteria. Bacteriophages are the most abundant **biological entity** in existence, and are bacteria's deadliest natural predator.

BIOLOGICAL ENTITY

An individual being which is connected to living things, or is itself a living being. While viruses share many qualities with living beings, they are not technically considered to be alive—an idea which will be expanded upon in sections to come.

USING PHAGES TO FIGHT BACTERIAL INFECTIONS

Phage therapy is based on the idea that we can use these bacteria-killing viruses to target bacterial infections in humans and other animals. Phage therapy also has huge potential to help us fight antibiotic resistance.

One of the key advantages with using phages is that many infect only a limited range of **bacterial strains**. When we use phages against a bacterial infection, we can specifically target the bacteria that are most resistant to current antibiotics. In doing so, we can reduce the number of bacteria types who are exposed to a given treatment, which gives them fewer chances to adapt and develop resistance. Phages' pickiness is also useful because it allows us to target only the harmful bacteria and leave the rest of our microbiome—the beneficial bacteria and other organisms that live in our bodies—intact. General antibiotics aren't picky in this way, meaning they may allow more species of bacteria to develop resistance, and could also harm our microbiome in the process.

At the same time, we must remember that antibiotics are one of the most important advances in modern medicine. While general antibiotics can harm the good and healthy bacteria of our bodies, the fact that they are not picky also means that they can attack a wider range of harmful bacteria. Antibiotics have been necessary to reduce the death rate of bacterial infections, and also to make other medical procedures like cancer treatment, surgery, and even childbirth much safer. If you have ever had strep-throat, pneumonia, or a staph infection, there is a good chance you have taken antibiotics yourself. But, given the scale of the antibiotic resistance problem, it is important that we look into possible medical alternatives. By uncovering the many mysteries of phage-bacteria dynamics, researchers like Maxwell can help us bring phage therapy “to life”.

BACTERIAL STRAIN

A subgroup of a bacterial species. For example, some strains of the bacteria E. Coli can give you food poisoning and make you sick, whereas many others live safely and naturally in your body.

HOW PHAGES USE BACTERIA TO REPLICATE

A key difference between bacteria and viruses more broadly is that, while bacteria can reproduce on their own, viruses can only create more copies of themselves by taking over another organism's cell, which is then called its host cell. The fact that viruses require another cell's machinery to replicate is one of the reasons that phages are not technically considered to be living things. When a phage wants to reproduce, it attaches onto a bacterium and injects its genetic material (**DNA or RNA**) into its host. The genetic material can then use the bacterium to produce more phages.

In **lytic replication**, the phage's genetic material immediately takes the bacterium hostage, forcing the cell to redirect its resources toward producing new phages (**Figure 2**). Eventually, the bacterium becomes so full of phages that it bursts and dies, which distributes the phages to other bacteria and allows the cycle to start over again.

In **lysogenic replication**, on the other hand, the phage becomes a kind of microscopic sleeper agent, quietly inserting its genetic material into the bacterium's **genome** and waiting for a particular trigger before starting a new lytic replication cycle (**Figure 3**). These sleeper agents are called prophages, and because they are part of the bacterium's genes, they can be passed on to future generations of bacteria when the bacterial cell divides.

DNA VS. RNA

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are two ways organisms and other biological agents store instructions that tell cells how to make proteins. These instructions help determine how we develop and function: they make us who we are. A virus can have either DNA or RNA, but never both at the same time.

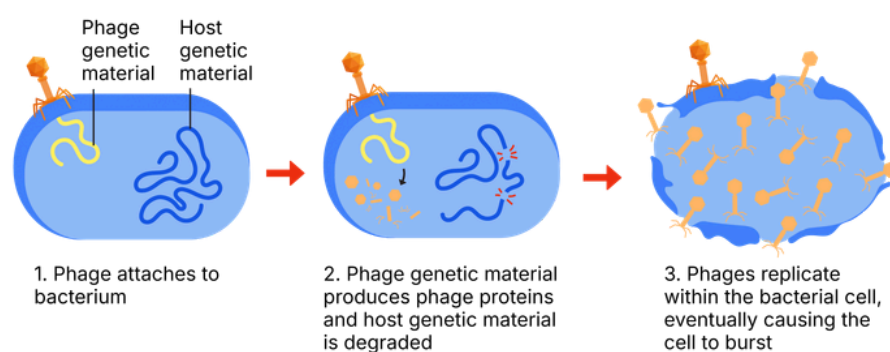
GENOME

The complete set of an organism's genetic material.

FIGURE 2

In lytic replication, the phage genetic material produces phage proteins inside the cell. The production of replicates leads to eruption of the cell.

Lytic replication



Lysogenic replication

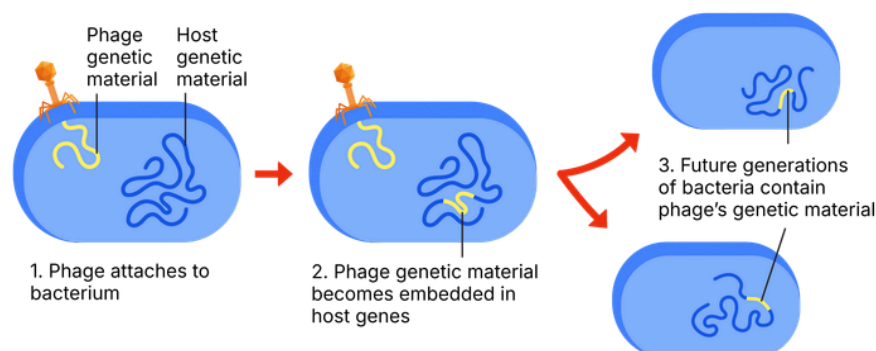


FIGURE 3

In lysogenic replication, the genetic material of the phage integrates into the bacterium's genetic material. Each new generation of the bacteria now contains phage genetic material.

PHAGE-BACTERIA COMBAT

Bacteria can use chemical weapons

Given that phages have been around for billions of years, it is not surprising that bacteria have evolved a number of different anti-phage defense mechanisms. For example, some bacteria will change the outer surface of their cells to prevent phages from injecting viral genetic material, almost as though they are putting on a suit of armour. Other bacteria have learned to sacrifice themselves once they realize they've been infected, in order to prevent the phages from reproducing and attacking other bacteria. Despite this diversity, many of these defence mechanisms were thought to rely on large **protein complexes**, which bacteria make by combining proteins and other cell parts.

However, Maxwell and her team demonstrated that in addition to using and producing protein complexes, bacteria can make a smaller chemical compound, called a **metabolite**, to protect themselves against phages. The team specifically looked at soil bacteria called *Streptomyces*, and found that they produce metabolites which prevent phages from reproducing properly. The metabolites interfere with phage DNA at an early stage in the phage's reproductive life cycle—a stage which is common to nearly all phage species. This finding suggests that bacterial metabolite production could protect against a wide variety of phages. We had known before that bacteria of many kinds produce these **metabolites**, but until Maxwell's work, we didn't understand why. We now know that it is a defense mechanism against phages, opening up a whole new line of questioning about bacteria's chemical defense.

Phages can prevent bacteria from talking to each other

Beyond the chemicals they use to prevent phage replication, bacteria also use chemical signals to communicate and coordinate their behaviour in a process known as **quorum sensing**. This form of communication relies on molecules released by the bacteria called **autoinducers**. Autoinducers accumulate as more bacteria are present, and the abundance of these molecules enables bacteria to detect when they are surrounded by many neighbours (**Figure 4**). With quorum sensing, bacteria detect a high concentration of autoinducers, and this tells them that it is time to unite and fight back against phages. One of the strategies that quorum sensing allows bacteria to do, for example, is to collectively change their cell surfaces. In a sense, the bacteria put up a collective shield, making it harder for phages to attack the group and inject their genetic material.

PROTEIN COMPLEX

Different chains of amino acids (the building blocks of protein) or other components of a cell linking with one another and forming a larger structure which can perform tasks.

METABOLITE

A small molecule produced during or as a result of some metabolic process, such as digestion or a chemical reaction within the body.

QUORUM SENSING

A form of chemical communication between bacteria with which they can coordinate their behaviour as a group.

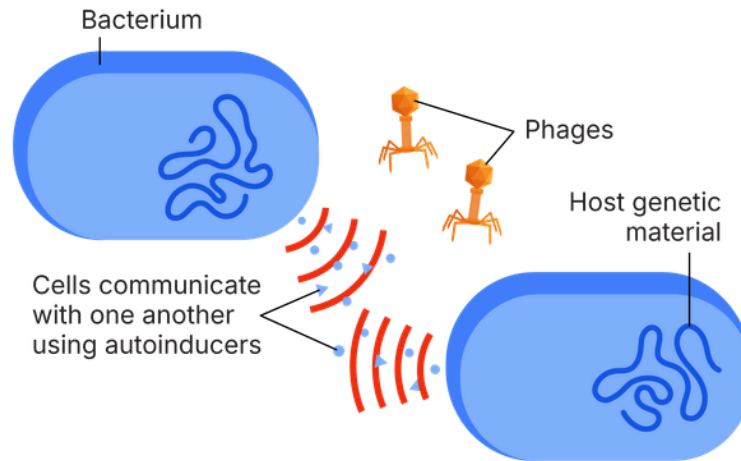
AUTOINDUCER

Chemical released by bacteria specifically for the purpose of coordinating behaviour in a group of bacteria.

Quorum sensing

FIGURE 4

Bacterial cells release molecules called autoinducers, which alert other cells that phages are present.



Unfortunately for bacteria, some phages have found ways to use quorum sensing to their advantage. Maxwell discovered a phage protein that can interfere with communication in its target bacterium, *P. aeruginosa*. This protein targets a part of bacteria that regulates many quorum-sensing behaviours. As a result, bacteria have a much harder time communicating and coordinating their defences against phages as a group. Maxwell's discovery may allow scientists and doctors to develop new ways to interfere with bacterial communication during infections. The idea here is that, if we can prevent bacteria from communicating, we may have an easier time fighting bacterial infections.

Maxwell demonstrated that phages not only target quorum-sensing to prevent bacterial coordination, but actually use bacterial quorum-sensing signals to support their own coordination. Phages use the chemical signals to send newly-produced phages only to bacteria that haven't yet been infected, making their attacks more efficient and widespread while reducing the number of phages that get wasted. This method was termed the “**anti-Kronos effect**” to signify how the technique helps preserve phage offspring—unlike Kronos, the ancient Greek god after which the method has named, who was known for eating his own children.

Maxwell's research also showed that phages can change the surface of their host cell to help them transmit their genetic material more easily, a property which had only been observed in other kinds of viruses. In understanding the phage-bacteria conflict better through these discoveries, we may also be able to improve the delivery of phage-based treatments.

Bacteria can use viral genetic information to their advantage

Though prophages can eventually become active and begin a lytic replication cycle—thus killing the host—Maxwell discovered that prophages can, in some cases, protect their host bacteria from contracting a different viral infection. She and her team first called attention to this phenomenon in 2016, and in 2024, they further refined the idea, demonstrating that a protein produced from prophage DNA could block the replication of a different phage, effectively turning a former viral invader into part of the bacterium's immune system. This finding highlights that the relationship between bacteria and phages is far more complicated than a simple battle between predator and prey.

MAXWELL'S RESEARCH: IMPORTANT FOR THEORY AND PRACTICE

As we mentioned, phages are pretty picky about which bacteria they attack. Even bacteria that belong to the same species can differ from one another, and it can be difficult to know exactly which strain is causing an infection. Phage therapy requires that we match the phage to the bacterial strain, and if we don't know which strain we're fighting against, it could be difficult to target the infection properly.

Luckily, people like Maxwell will continue to uncover the mysteries of phage-bacteria combat, which will not only help us improve our phage-based medications, but will help us fight antibiotic resistance more broadly. In her lab, Maxwell leads the next generation of scientists forward, paving the way for future researchers and demonstrating that her impact will be felt for many years to come.

Article written by Leanne Cherry

Illustrated by Heather Ng-Cornish

This article has been reviewed by Dr. Karen Maxwell and colleagues for accuracy and accessibility.

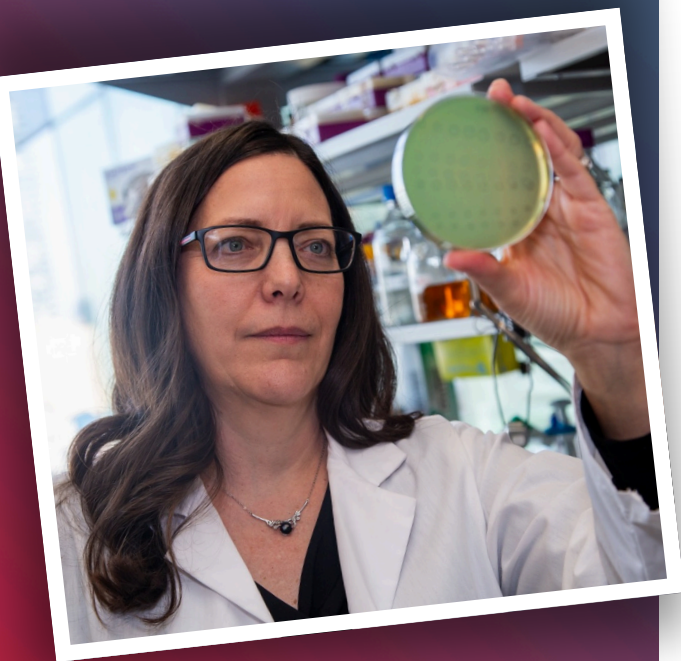


“

A lot of what we do as scientists is challenge each other. We poke holes in each other's arguments, and that's what science is all about. So, I think students need to have confidence in themselves and confidence in their ideas, but also be resilient enough that when people point out problems with your science, you're strong enough to withstand it.

”

- Karen Maxwell



MEET THE SCIENTIST: Dr. Karen Maxwell

Karen Maxwell is a professor in the Department of Biochemistry at the University of Toronto and holds a Tier 1 Canada Research Chair in Bacteriophage Biology and Therapeutics. She earned her Ph.D. in Molecular Genetics at the University of Toronto and completed postdoctoral research at the Ontario Centre for Structural Genomics. Her laboratory studies interactions between bacteria and the viruses that infect them, known as bacteriophages or phages. By investigating how phages infect bacteria and how bacteria defend themselves, her research is helping scientists better understand these complex relationships and explore how phages could be used to combat antibiotic-resistant bacterial infections.



YOUTH ACCESSIBILITY REVIEW

This article was reviewed by students through the Canadian Association for Girls in Science (CAGIS)—Canada’s largest and longest-running STEM (science, technology, trades, engineering, and math) club for girls and gender-diverse youth aged 7-17. This award-winning club, founded in 1992, supports interest in STEM with virtual programming and local clubs that visit labs, workshops, and field sites to meet mentors and do fun, hands-on activities. Their thoughtful feedback on clarity, accessibility, and reader engagement helped shape the final version of this article and ensure it is engaging and accessible for youth readers.



Adrienne Ma • Grade 12

“I hope to pursue a career in optometry to combine my love for helping others and my fascination for the human eye.”



Deepa Kalia • Grade 12

“I hope to combine my love of technology with my passion for business and explore how technology can be used to create innovative solutions and opportunities.”



Raneem Salah • First-year university

“I’m excited to study human biology and find ways to impact society using that knowledge!”



Vienna Cipparrone • First-year university

“I am intending on studying neuroscience and psychology, and I want to explore how psychological disorders affect brain structure and function.”



A SHOCK TO THE SYSTEM: RESTORING BLOOD PRESSURE FUNCTION AFTER SPINAL CORD INJURY

DR. AARON PHILLIPS

PETER GILGAN CANADA GAIRDNER MOMENTUM AWARD
WINNER

Associate Professor, Departments of Clinical Neurosciences, Cardiac Sciences, Physiology and Pharmacology, University of Calgary; Associate Dean, Innovation and Commercialization, Cumming School of Medicine, University of Calgary, Canada

SUMMARY

Aaron Phillips' research aims to help people with spinal cord injuries (SCI) reduce the challenges and risks associated with blood pressure dysfunction—a common but often overlooked complication of SCI. Over the course of several studies, Phillips identified which specific regions of the nervous system are most important for blood pressure regulation. From there, he developed a device that can be implanted in the spinal cord which monitors blood pressure in real time and sends electrical signals to the nervous system, helping to restore normal blood pressure.

STUDENT REVIEWERS:



CELINE
Grade 10



HARGUN
Grade 10



RHYTHM
Grade 8



ROSE
Grade 9

While many people associate spinal cord injuries (SCI) with losing the ability to walk, SCI patients tend to focus on a much lesser-known side effect of this injury: **blood pressure dysfunction**. SCI often prevents the nervous system from sending the messages needed to effectively manage blood pressure—the metric for how much force the blood exerts against the walls of the blood vessels. Issues with this system can immediately lead to a heart attack, and over time can increase a person's risk of heart problems, impair their brain functioning, and lower their chances of survival overall. Blood pressure dysfunction is particularly troublesome for SCI patients because it can inhibit their ability to sit upright, making treatment and social situations more challenging.

Dr. Aaron Phillips, Professor and Researcher in Clinical Neuroscience at the University of Calgary, is conducting research to fight back against these issues.

After mapping the circuits of the nervous system that influence blood pressure, Phillips developed a device for the spinal cord which monitors blood pressure in real time and sends messages to the circuits he identified. Over the course of several studies, Phillips showed that his device could restore SCI patients' blood pressure control within hours after it was implanted, and continue doing for as long as it is implanted. As Phillips' device begins to receive approval for widespread medical use, it holds the potential to improve the livelihoods and lifespans of millions of people living with SCI worldwide.

HOW BLOOD PRESSURE IS CONTROLLED

To better understand Phillips' work, it is helpful to first understand how the nervous system functions and how it influences blood pressure (Figure 1).

The nervous system is essentially a series of connected wires through which electrical signals can travel, spanning from the very tips of your toes to the neurons in your brain. These signals allow you to coordinate and control your movements, to interpret information from your environment like light and sound, and to regulate unconscious processes like breathing, heart rate, and blood pressure. Almost all of these wires travel through the spinal cord as the central "highway", transmitting information from the brain to body and vice versa.

The body's process for regulating blood pressure has several moving parts. When you exercise, for example, your muscles require more oxygen and nutrients, so your nervous system works with your heart and blood vessels to raise your blood pressure and deliver more oxygen-rich blood around the body. Blood pressure can be affected by something as simple as your body's position. When you transition from sitting to standing, gravity pulls your blood towards your legs, which can briefly lower your blood pressure. But, as soon as the nervous system detects this change, a reaction called the **baroreflex** will kick in. The baroreflex instructs the heart to pump harder and the blood vessels to squeeze tighter, ultimately restoring blood pressure to normal levels.

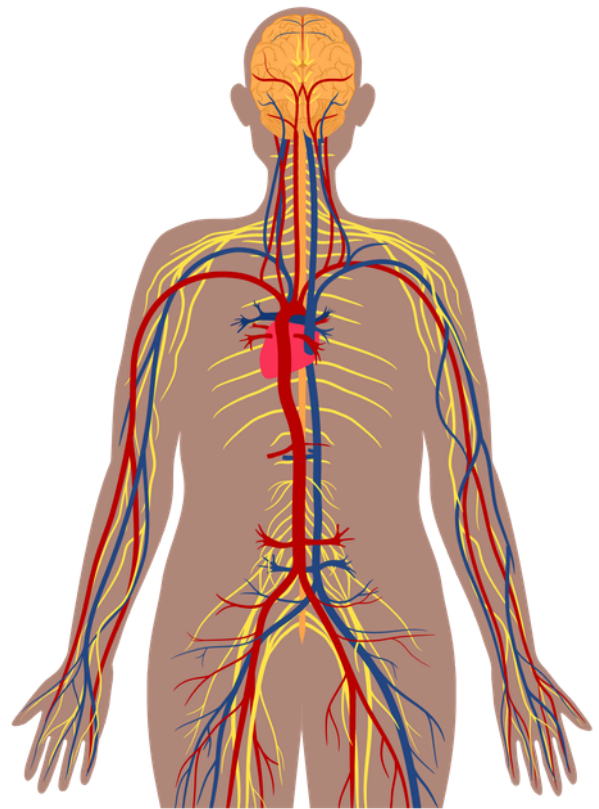


FIGURE 1

A diagram of the nervous system (yellow) and circulatory system (blue and red) from a rear view of the human body.

MOTOR COMMANDS

Signals sent from the brain through the spinal cord that direct muscles to contract, relax, and coordinate movement. These signals turn the brain's plans, such as standing or walking, into physical actions.

The baroreflex depends on the heart and nervous system working in harmony. These systems therefore must be able to communicate with each other. When the spinal cord is damaged, the primary highway for delivering **motor commands** from the brain and sensory information from the body is blocked off, making any attempts at communicating much more difficult. The degree to which the road is blocked depends on the location and severity of the injury, but generally speaking, the systems below the site of the injury are the most affected. This is why a person with an SCI to the lower spine may lose the ability to walk, but may maintain control over their torso and arms.

For blood pressure dysfunction, even if an SCI patient's nervous system detects a change in blood pressure, the damaged connection in their spine may prevent the nervous system from sending the motor commands needed to restore it. However, this does not mean the circuit is incapable of carrying electric messages altogether. It just means that we have to change where the message is coming from.

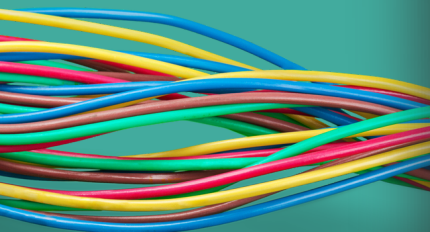
UNCHARTED TERRITORY: MAPPING THE NERVOUS SYSTEM'S BLOOD PRESSURE CIRCUITS

To solve the problems associated with spinal cord injury and blood pressure dysfunction, Phillips first needed to figure out where blood pressure regulation circuits are located in the nervous system. For this, he leveraged something called **epidural electrical stimulation (EES)**, a medical technique for externally supplying electricity to an SCI patient's nervous system. EES works by implanting tiny metal pins called electrodes beneath the damaged section of a patient's spinal cord and running electricity through the electrodes. This enables electricity to reach areas of the nervous system below the severed connection, which can ultimately restore some of its functioning.

Phillips and his team conducted a number of EES experiments to chart blood pressure regulation in the nervous system. Many of these experiments measured something called the **pressor response**, which is a sudden and dramatic increase in blood pressure triggered by stimulation of the nervous system. The researchers began by placing electrodes in different areas of the spine to figure out which one elicited the strongest pressor response. They found that blood pressure increased most when stimulated near the middle of the spine, suggesting that key blood pressure control circuits were in this area.

EPIDURAL ELECTRICAL STIMULATION (EES)

A technique that uses electrodes implanted near the spinal cord to deliver controlled electrical signals and activate specific nerve circuits.



The fact that EES increased blood pressure when applied in this area has to do with the division of the nervous system. The nervous system has two main branches: **the central branch**, which is composed of the brain and spinal cord, and **the peripheral branch**, which is composed of all the other neurons around the body. The peripheral branch itself has many different sub-branches, with blood pressure primarily being regulated by a sub-branch called the **sympathetic nervous system**. This sub-branch is known for activating the fight-or-flight response in the face of danger, and part of how it prepares the body for action is by increasing heart rate and blood pressure.

As Phillips parsed through blood pressure regulation circuits in the nervous system, he found that sympathetic neurons were densely populated near the middle of the spine—the area that they had previously shown to induce the greatest pressor response when stimulated with EES. The team called these densely populated areas “**haemodynamic hotspots**” because stimulating them could produce changes in blood pressure and blood flow.

Next, Phillips and his team had to figure out which exact path the signals from EES took to induce a blood pressure response. It turns out that the pressor response depends on the complex interplay of several different kinds of neurons.

There are over 86 billion neurons in the brain alone, but they can be broadly grouped into three categories: **sensory neurons**, which detect information from the body and environment; **motor neurons**, which send signals that control movement and other bodily functions; and **interneurons**, which act as bridges, passing signals between different neurons. Interneurons turned out to play an important role in understanding how blood pressure is regulated.

HAEMODYNAMICS

The movement of blood through the body and the forces, including blood pressure, that influence it.



EES signals first travel through sensory neurons. These neurons tend to be closer to the outer surface of the spine, where the electrodes are placed, and they are particularly responsive to electrical stimulation. The researchers confirmed that sensory neurons were important for blood pressure during some of their early experiments working with mice; when they prevented signals from travelling through these neurons, EES no longer induced a pressor response.

After passing through sensory neurons, the electric signals go through sympathetic interneurons—rather than going directly to the sympathetic motor neurons that control blood pressure. Phillips and his team uncovered this pathway after observing that there were no direct connections between the sensory neurons and the sympathetic motor neurons. Finally, the signals travel from the interneurons to the sympathetic motor neurons, where they cause a chemical release which instructs the blood vessels to contract. This ultimately increases blood pressure (**Figure 2**).

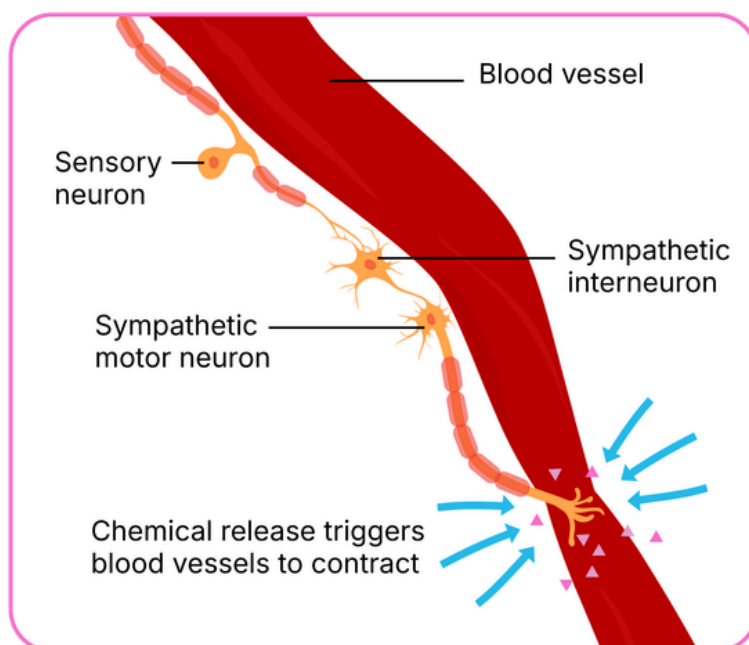


FIGURE 2

Three types of neurons connect and transmit the electrical signal, ending at the sympathetic motor neuron which causes a chemical release.

By studying large segments of the spine, tiny clusters of individual neurons, and all of the pathways in between, Phillips and his team were able to map precisely which parts of the nervous system regulate blood pressure—and how we might be able to control and restore them after SCI.

CONTROLLING BLOOD PRESSURE ELECTRONICALLY

To regulate blood pressure using an external device, it is important that we mimic the body's natural regulatory signals as closely as possible. Otherwise, we risk causing further damage to the nervous system, as well as introducing more problems to circulation. To achieve these natural patterns, Phillips recorded the nervous system's natural blood pressure signals and encoded them into the EES implant. This would ensure that signals produced by the implant are similar in length, frequency, and strength to the signals that would normally emerge from the nervous system.

Another key feature of this device is that it operates in closed loop, meaning it constantly monitors a patient's blood pressure and updates its output accordingly. For example, if an SCI patient were to transition from lying down to sitting up, their blood pressure may temporarily drop. The implant would detect this change, and it would send electric signals that cause the blood vessels to squeeze, ultimately restoring blood pressure. This implant is a kind of neuroprosthetic—a device that can be used to restore some lost function of the brain and nervous system. This is similar to how a prosthetic leg can help restore one's ability to walk after amputation. Phillips' implant works very similarly to our body's natural blood pressure reflex—the baroreflex—and has since been termed the “neuroprosthetic baroreflex”.

Phillips ran several trials to assess the device's effectiveness, beginning by testing it in mice and eventually working up to using it in human patients with SCIs. The results showed the same thing across all species: By placing the neuroprosthetic baroreflex over the spinal regions that Phillips identified, Phillips' device can correct both the immediate and long-term blood pressure dysfunction associated with SCI.

IMPACT FOR SCI PATIENTS AND BEYOND

Before the invention of the neuroprosthetic baroreflex, many of the treatments—or, more accurately, management techniques—for blood pressure dysfunction in SCI were uncomfortable for the patient and ineffective at dealing with the problem in the long run. These management techniques include consuming a diet high in salt or wearing a compressive sleeve around the torso to keep blood pressure elevated, among other measures. Phillips analyzed survey data from over 1400 SCI patients, and he found that even those who used these management techniques were still often left with dizziness, blurred vision, and overall feelings of weakness—all of which are symptoms of blood pressure dysfunction. Phillips' neuroprosthetic baroreflex was shown to alleviate these issues by sending signals that mimic and subsequently restore the body's natural blood pressure regulation processes, even in the face of a damaged spinal cord.

Beyond its applications in SCI treatment, Phillips' device could also potentially be effective for treating blood pressure regulation issues more broadly. Indeed, high blood pressure affects billions of people without SCIs. Phillips and his team are currently conducting research to understand how something like the neuroprosthetic baroreflex could help restore blood pressure functioning for people around the world. While this has yet to be applied in practice, Phillips' work takes us one step closer to getting there.

Article written by Leanne Cherry

Illustrated by Heather Ng-Cornish

This article has been reviewed by Dr. Aaron Phillips and colleagues for accuracy and accessibility.

MEET THE SCIENTIST: Dr. Aaron Phillips

Aaron Phillips is a professor at the University of Calgary whose research focuses on restoring cardiovascular function after spinal cord injury. His interdisciplinary work combines neuroscience, cardiovascular physiology, bioengineering and clinical research. Phillips and his team identified regions of the spinal cord involved in blood pressure control, helping reveal how spinal cord injury can disrupt the body's ability to maintain stable blood pressure. Building on these discoveries, he has developed a "neuroprosthetic baroreflex," which uses targeted spinal cord stimulation to help restore blood pressure control. His research is advancing new approaches to treating autonomic dysfunction and improving health and rehabilitation for people living with spinal cord injury.



YOUTH ACCESSIBILITY REVIEW

This article was reviewed by high school students through the Canadian Association for Girls in Science (CAGIS)—Canada's largest and longest-running STEM (science, technology, trades, engineering, and math) club for girls and gender-diverse youth aged 7-17. This award-winning club, founded in 1992, supports interest in STEM with virtual programming and local clubs that visit labs, workshops, and field sites to meet mentors and do fun, hands-on activities. Their thoughtful feedback on clarity, accessibility, and reader engagement helped shape the final version of this article and ensure it is engaging and accessible for youth readers.



Rhythm Sehgal • Grade 8

"I hope to study Health Science and Genomics to make new discoveries in healthcare."



Rose Isakson • Grade 9

"I hope to study biology, particularly animal behaviour."



Celine C.A. Chen • Grade 10

"I hope to study biomedical informatics and enjoy learning about how technology can improve healthcare."



Hargun Kaur • Grade 10

"I'm interested in environmental science and how STEM can help create a more sustainable future."



PREVENTING PROTEIN MISFOLDING: THE BATTLE AGAINST TOXIC PROTEIN CLUMPS

PROF. JEFFERY W. KELLY

CANADA GAIRDNER INTERNATIONAL AWARD WINNER

H. Lutchter Brown Professor of Chemistry, Department of Chemistry, Scripps Research, La Jolla, United States

SUMMARY

Prof. Jeffery W. Kelly was the first person to develop a medication that successfully slowed the progression of a human amyloid disease—a kind of disease which occurs when our proteins undergo shape or structural changes, allowing them to misassemble and accumulate in clumps throughout the body causing organ damage. Kelly was also the first to show that we can prevent some of the harmful effects of these diseases if we can stop the proteins from undergoing shape changes forming clumps in the first place. Kelly's work represents a massive step forward in our conceptual understanding and our treatment methods for these diseases.

STUDENT REVIEWERS:



ARSHIA
Grade 11



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Amyloid diseases occur when abnormally-shaped proteins build up around the brain and body and form toxic clumps, called **amyloid aggregates**. Over time, amyloid aggregates degrade a person's health, often leading bodily dysfunction and deterioration, and eventually, death. While amyloid diseases are difficult to study, researchers have made huge progress in understanding their underpinnings, in some cases even treating them.

Prof. Jeffery W. Kelly, a chemistry professor at *Scripps Research Institute* in California, created the first ever medication to successfully slow the progression of a human amyloid disease. More specifically, Kelly designed a drug to help manage **Transthyretin amyloidosis (ATTR)**—the third most common amyloid disease, behind Alzheimer's and Parkinson's diseases. ATTR occurs when the protein transthyretin forms into amyloid aggregates around the heart and nerves.

AMYLOID AGGREGATION

The process of misfolded proteins becoming the toxic clumps called amyloid aggregates.

AMINO ACID

Chemical building blocks which join together to form protein. In the case of transthyretin, the amino acid chains first form into the smaller monomers, and then the four monomers come together to create transthyretin.

Kelly developed the drug after a foundational discovery made in his laboratory: that changes in a protein's shape or structure are enough to kickstart toxic protein build-up. Beyond slowing the progression of ATTR, Kelly was also the first to definitively prove that **amyloid aggregation** fuels neurodegeneration—the loss of neurons in the brain and/or outer nervous system often seen in amyloid diseases. Kelly's discoveries have propelled the study of human amyloid disease forward, fundamentally changing how we think about research and drug development in this field.

WHEN A PROTEIN'S STRUCTURE BECOMES HARMFUL

The **transthyretin protein** is made of four identical pieces, called monomers, that join together to form a single protein. Transthyretin is a kind of transport protein, and its function is to deliver hormones and vitamins around the body.

Our cells make proteins by stringing together several small molecules called **amino acids**. Normally, this string of amino acids folds to produce a protein of a specific 3D structure which ultimately allows a protein to do its job. With ATTR, however, a person's transthyretin protein becomes unstable and splits into individual monomers, meaning transthyretin loses its proper structure. When detached, the monomers can misfold into abnormal shapes which form large assemblies or clumps with other misfolded monomers (**Figure 1**). The bonds holding these clumps together are incredibly strong, making it difficult for our bodies to break them down.

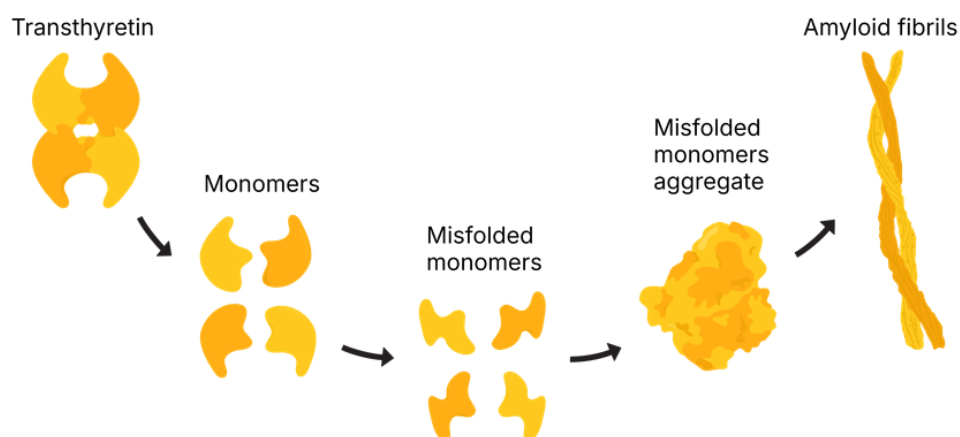


FIGURE 1

Transthyretin proteins split into monomers. The monomers misfold and aggregate which create amyloid fibrils.

Over time, these misfolded protein clumps build up around the heart and throughout the nervous systems, forming amyloid aggregates and leading to issues like irregular heartbeat, shortness of breath, and tingling and numbness of the toes and feet (**Figure 2**). Because these symptoms are common to many other illnesses, ATTR can be difficult to diagnose. If left untreated, it will ultimately lead to death.

UNCOVERING THE HARM OF AMYLOID AGGREGATES

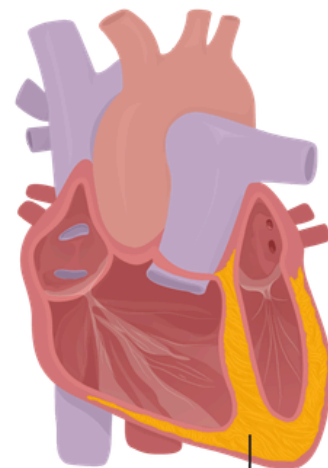
Kelly was the first to prove that transthyretin aggregation is responsible for the neurodegeneration seen in ATTR. He discovered this by revealing something about our DNA—the molecular information encoded deep within us that makes us who we are.

NA is grouped into segments called genes. Some genes act as instruction manuals for building particular proteins, telling our cells which amino acid to use and where to place it when creating a protein. A protein's amino acids determine the protein's final structure and function, and any change to the order of amino acids—or the underlying instruction manual—can completely alter how the protein will form.

Humans generally have two copies of every gene, with one coming from each parent. One of the ways a person can develop ATTR is through a mutation to one copy of the gene which codes for the transthyretin protein, passed down through their family tree.

This version of ATTR is called hereditary or **variant ATTR (ATTRv)**. For someone with ATTRv, a genetic mutation on one copy makes the transthyretin protein highly unstable. It breaks apart into monomers more easily, which can ultimately lead to the formation of amyloid aggregates that damage the body.

However, during his research, Kelly noticed a different mutation that can occur on the transthyretin genes—one which seemed to prevent the harmful effects of ATTR from developing. In rare cases, people with ATTRv can have mutations in both gene copies: one mutation that leads to amyloid aggregation and one that is protective against amyloid disease. Kelly found that people who had both mutations did not show the typical neurological symptoms of the disease. It turns out that this second mutation counteracted the effects of the first by stabilizing the transthyretin protein. Because the protein remained stable, it was much less likely to break into monomers, therefore preventing it from misfolding and clumping with other monomers to form amyloid aggregates.



Amyloid aggregates
in the myocardium

FIGURE 2

Amyloid fibrils (yellow) build up in the myocardium of the heart.

By showing that preventing aggregation also prevented disease symptoms, Kelly demonstrated that amyloid aggregates are a key driver of nerve damage in ATTR. Using what he discovered here, Kelly was then able to figure out how to create a medication that would slow ATTR's progression down—and he was the first person to ever do so.

THE IDEA BEHIND KELLY'S MEDICATION

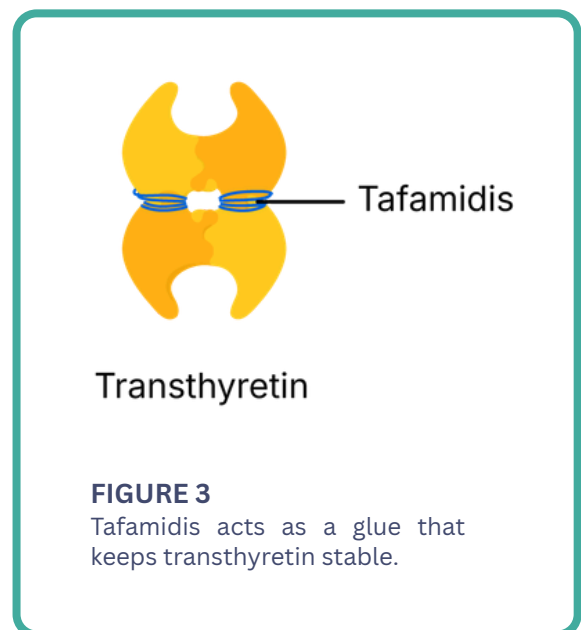
Tafamidis, the ATTR drug that Kelly created, essentially keeps its target protein transthyretin intact. Because transthyretin is a transport protein, it contains various sites that different molecules can bind to. Two of these sites are right at the centre of the protein's four subunits. When one or two small molecules bind here, they act almost like a glue for transthyretin, holding its four subunits together. When this site is empty, the protein is naturally less stable, but under normal conditions this does not cause any issues. However, for someone with ATTR, it is a completely different story.

As mentioned, ATTRv is caused by an inherited genetic mutation. A person can also develop ATTR as a result of aging, and in this case, it is called wild-type ATTR (ATTRwt). For these patients, their transthyretin is normal in terms of the amino acids comprising it, but it nonetheless misfolds and leads to amyloid aggregation upon aging for reasons that are not yet understood.

Kelly's idea behind his drug, tafamidis, was that it would bind to transthyretin's empty binding site(s). By acting like a molecular glue, it helps hold the transthyretin protein together to prevent it from falling apart, becoming misshapen, and misassembling into toxic amyloid aggregates (**Figure 3**). After formulating this theory, Kelly and his team ran several human clinical trials to find out how well the drug would work in practice.

They found that when ATTR patients took tafamidis, it slowed or stopped amyloid aggregation around the body, including in the nervous system and the heart. The early phases of these trials demonstrated that tafamidis helped slow neurodegeneration, while the final phases confirmed that tafamidis decreased death rate and reduced the number of hospitalizations due to ATTR-related heart issues.

Tafamidis has since been approved for usage in over 50 countries. Its effectiveness further confirmed the idea that amyloid diseases can be slowed by stabilizing proteins before they have a chance to fall apart and form aggregates.



BIGGER PICTURE: IMPACTS ON OTHER AMYLOID DISEASES

Beyond transforming the treatment of ATTR, Kelly's work fundamentally changed how scientists and physicians think about amyloid diseases more broadly. Researchers have long debated whether amyloid aggregation is the cause of the bodily degradation and organ system deterioration characterizing these diseases, or merely a symptom of a different underlying issue. Skepticism towards the aggregation hypothesis—which argued that aggregation into a spectrum of aggregates is the cause of the neurodegeneration seen in Alzheimer's disease—arose because of repeated failed attempts to treat neurodegeneration in Alzheimer's disease with medication.

Part of the difficulty with proving or disproving the amyloid hypothesis also has to do with where the amyloid aggregates form. In Alzheimer's disease, they form directly in the brain, which is part of the central nervous system. Brain tissue is not easy to study in living patients, and often we must wait until after a patient has died to actually see the aggregates. While we have imaging techniques that help us get around this today, many questions about Alzheimer's and amyloid aggregation remain unanswered.

However, ATTR is different from other amyloid diseases. Amyloid aggregation in ATTR starts in the heart and in the peripheral nervous system—the network of nerves that lies beyond our brain and spinal cord—only accumulating in the central nervous system as the disease progresses. The fact that the disease starts outside the central nervous system enabled Kelly to observe the toxic effects of ATTR's amyloid aggregates more easily than if he had been observing the effect of Alzheimer's aggregates, which is concentrated in the brain.

Kelly's discoveries about amyloid aggregates and his drug to combat them has now motivated the development and regulatory agency approval of nine additional protein aggregation inhibiting and/or modulating drugs. These slow down the progression of other amyloid diseases such as Alzheimer's.

The ability to ameliorate these diseases with medication represents a huge step forward in both our conceptual understanding of and our treatment for amyloid diseases. Thanks to Kelly and his team, ATTR patients are able to increase the quality and the length of their lives, and amyloid disease researchers now have a promising direction to head in when developing new medications for amyloid diseases currently lacking drugs.

Article written by Leanne Cherry

Illustrated by Heather Ng-Cornish

This article has been reviewed by Dr. Jeffery Kelly
and colleagues for accuracy and accessibility.



MEET THE SCIENTIST: Prof. Jeffery W. Kelly

Jeffery W. Kelly is the H. Lutcher Brown Professor of Chemistry at Scripps Research. He earned his Ph.D. in Chemistry from the University of North Carolina and completed postdoctoral training at Rockefeller University. His laboratory studies how proteins fold, misfold and aggregate, processes associated with amyloid and neurodegenerative diseases. Kelly's research on transthyretin amyloidosis led to the development of tafamidis, a medicine that slows disease progression by stabilizing the transthyretin protein and preventing its aggregation. His laboratory continues to investigate new treatments for diseases caused by protein misfolding. Kelly is a member of the U.S. National Academy of Sciences and American Academy of Arts and Sciences.



YOUTH ACCESSIBILITY REVIEW

This article was reviewed by high school students through the Canadian Association for Girls in Science (CAGIS)—Canada's largest and longest-running STEM (science, technology, trades, engineering, and math) club for girls and gender-diverse youth aged 7-17. This award-winning club, founded in 1992, supports interest in STEM with virtual programming and local clubs that visit labs, workshops, and field sites to meet mentors and do fun, hands-on activities. Their thoughtful feedback on clarity, accessibility, and reader engagement helped shape the final version of this article and ensure it is engaging and accessible for youth readers.



Arshia Nair • Grade 11

"I am interested in the science of neurodegenerative diseases, which fuels my desire to pursue a career in healthcare."



Cynthia Rayson • Grade 11

"I hope to study biomedical engineering and develop new dental technologies to enhance patient care."



Valini Parasram • Grade 12

"In the future I hope to study chemistry and its nuclear applications."



June Liu • Grade 12

"I aspire to pursue a career in healthcare or biomedicine with a focus on applied research and potentially business, re-imagining the way we approach real world issues with practical and innovative solutions."



PROTEOMICS: HOW WE KNOW WHAT WE KNOW ABOUT PROTEINS

CANADA GAIRDNER INTERNATIONAL AWARD WINNERS

Prof. Ruedi Aebersold

Professor Emeritus, Molecular Systems Biology, Institute of Molecular Systems Biology, Department of Biology, ETH Zurich, Switzerland

Prof. Matthias Mann

Director of Department of Proteomics and Signal Transduction, Max Planck Institute of Biochemistry, Martinsried, Germany

Prof. John R. Yates III

John Lytton Young Endowed Chair and Professor, Department of Integrative Structural and Computational Biology, Scripps Research, La Jolla, United States

SUMMARY

Proteomics is the large-scale study of proteins, which aims to identify, quantify, and understand what proteins do across all species. A significant portion of the field's progress over the years can be attributed to the work of Drs. John Yates III, Ruedi Aebersold, and Matthias Mann. These researchers each focused on separate but related proteomics problems: Yates worked on identifying proteins, Aebersold worked on quantifying them, and Mann worked on understanding proteins in the context of medicine. Their techniques are now practiced in proteomics labs around the world and have greatly expanded our knowledge of proteins.

STUDENT REVIEWERS:



ARSHIA
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Grade 12

At any given moment, there are approximately 10 trillion proteins in our bodies. Proteins are crucial for just about every aspect of our functioning, from providing structure to our muscles and organs to transporting messages and nutrients around the body. By uncovering what proteins do and how they function, proteomics researchers come closer to revealing how living systems work overall.

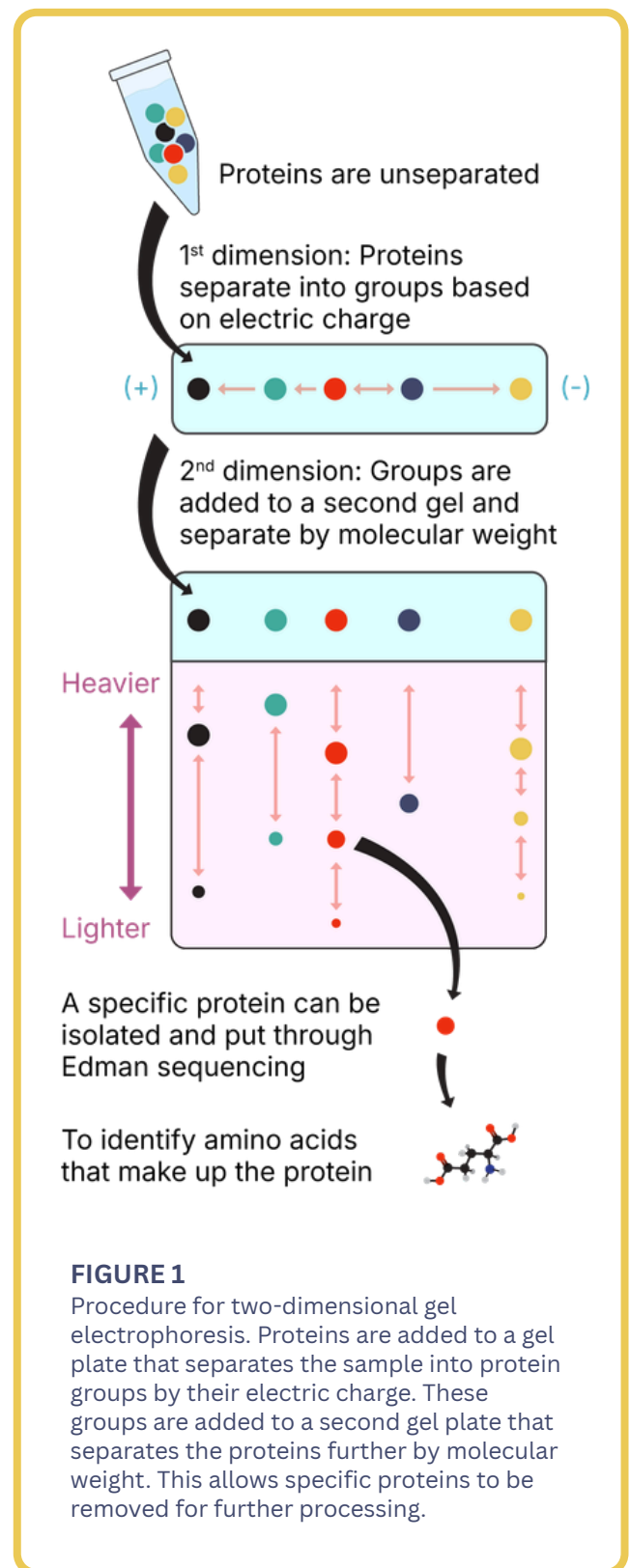
However, understanding how proteins work is no simple task. A single cell can contain approximately 8 billion proteins—a number that is similar to the number of people on Earth. Understanding the purpose, quantity, or state of any given protein can feel like searching for a needle in a haystack. Before researchers could begin to unravel proteins' many mysteries, they needed to have the right tools to do so.

Drs. John Yates III, Ruedi Aebersold, and Matthias Mann have each made immense contributions to proteomics, developing laboratory techniques to analyze, measure, and categorize proteins that inform much of what we know about proteins today. Researchers ask many different questions about proteins, but Yates, Aebersold, and Mann focused on three of the most pressing: How can we analyze and categorize proteins in large numbers? How can we accurately measure the total number of proteins in a sample? And how can we use this data to understand how proteins function in living beings?

BEFORE YATES, AEBERSOLD, AND MANN'S KEY DISCOVERIES

One of the first problems that proteomics researchers solved was that of rapidly uncovering a protein's amino acid sequence—the unique chain of chemical building blocks that make up a protein. Proteins that differ by even a single amino acid can have completely different functions and purposes in an organism, so knowing a protein's amino acid sequence is useful for identifying it and figuring out how it works.

Traditionally, proteins needed to be isolated from each other to be able to sequence their amino acids. In the 1970s and '80s, this was mainly accomplished using a technique called **two-dimensional gel electrophoresis (2DGE)**, which allowed scientists to take a complex mixture of proteins from a cell and separate them according to the **mass** and **electric charge** of each individual protein (**Figure 1**).



MASS

A fundamental property that determines how much matter is present in an object

ELECTRIC CHARGE

A fundamental property that determines how matter will behave in an electric field. Matter's charge is influenced by the ratio of positively and negatively charged particles it carries. Opposite charges attract whereas like charges repel.

The result of running 2DGE on this large collection of proteins would be an array on a gel comprised of thousands of different spots, each one containing one or several proteins of a particular mass and electric charge.

From there, scientists could remove the spot from the gel and use a technique called **Edman degradation sequencing** to uncover its amino acid sequence. Edman sequencing was the first major advance for protein sequencing as it automated a process of sequentially removing amino acids from the front of a protein. By removing amino acids one at a time you could learn the sequence of the protein. When used on an intact protein, Edman sequencing could reveal the first 25-30 amino acids of the protein's sequence.

These techniques were not perfect. While 2DGE was good at separating proteins with stark differences in mass and charge, there are many kinds of proteins with similar mass and charge that have different identities. These frequently ended up in the same spot on a 2DGE gel, making it difficult to figure out an individual protein's amino acids using Edman sequencing. Even when you were able to get a relatively pure protein spot from 2DGE, Edman sequencing was painstakingly slow and labour intensive. Furthermore, about half of all human proteins have a modification on their first amino acid that prevents Edman sequencing from being carried out.

A major advance in protein sequencing was the use of a technique called **tandem mass spectrometry** (aka **MS/MS**). A mass spectrometer—the instrument used for MS/MS—measures the mass and electric charge of molecules, allowing scientists to identify them. When MS/MS was first used for protein sequencing, researchers would often begin by separating proteins with 2DGE. They would then choose a particular spot from the 2DGE plate, and break its proteins down into smaller pieces called **peptides**. These would be analyzed by MS/MS.

MS/MS blasts the peptides with a gas that breaks the peptides into fragments of different masses and electric charge. These fragments form a distinct pattern, effectively becoming a peptide's fingerprint (**Figure 2**). The pattern can be interpreted to identify the peptide, and by analyzing all the peptides created by digestion of the protein, the sequence of the intact protein can be reassembled like a jigsaw puzzle.

Peptides and proteins are both fundamentally the same thing: a chain of amino acids. They differ mainly in term of size and structure. Peptides are smaller (2-50 amino acids), whereas proteins are larger (50+ amino acids) and fold into more complicated structures.

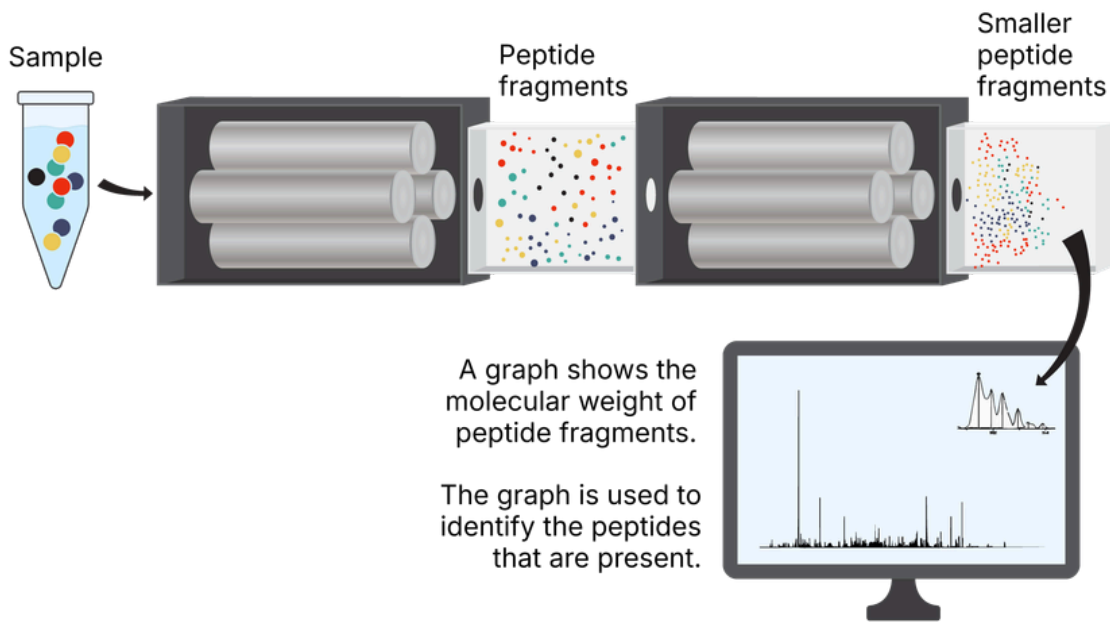


FIGURE 2

A tandem mass spectrometer. “Tandem” means “two” mass analyzers. The sample moves through the first mass analyzer to produce fragments. The fragments pass through a second mass analyzer to produce even smaller fragments. The mass of these fragments is read by a computer, which provides information on the peptides that are present in the sample.

JOHN YATES: IDENTIFYING PROTEINS AT SCALE

Yates has made many important contributions to the field of proteomics, but the most groundbreaking of these has to do with his use of MS/MS.

MS/MS sequencing experiments produce many peptide fragmentation patterns, and researchers were initially stuck manually interpreting these patterns to identify each peptide derived from their protein of interest. This process was time-consuming and difficult. To make this more efficient, Yates drew data from a massive scientific endeavour that began in the early 1990s: the **genome** sequencing projects.

At this time, researchers around the world were attempting to sequence every organism’s genome—the entirety of an organism’s DNA. A protein’s amino acid sequence is determined by the instructions encoded within an organism’s DNA, and their genome thus represents all of the instructions from which proteins are constructed. Yates recognized this data could help uncover peptides’ amino acid sequences.



John R. Yates III

GENOME

All of an organism's genetic information (i.e. the entire set of their DNA), containing all of the instructions necessary to develop and live and ultimately shaping the organism as an individual being.

Using genome data, we can generate an image of how a peptide might fragment in a theoretical MS/MS experiment. Because the image is generated directly from the genome data, we would also know the amino acid sequence associated with this theoretical fragmentation pattern. Yates created **SEQUEST**, a computer algorithm that matched *real* MS/MS peptide data against this *theoretical* peptide fragmentation pattern created from genome sequence data.

SEQUEST made it so that researchers didn't have to sequence a protein's entire amino acid sequence to identify it. Rather, they could observe a few of its peptide fragments and the algorithm would match the fragments to a known protein in the genome sequence database. Overall, this made it much easier for researchers to identify all the proteins in a sample.

Even with SEQUEST though, MS/MS had yet to reach its full potential. Many proteomics researchers were still using 2DGE as a precursor to mass spectrometry analysis, which still had the problem of containing multiple proteins in each sample. Moreover, analyzing individual spots one at a time was slow. This made it particularly hard to identify large numbers of proteins from the gel and to find the less abundant proteins of a sample. For example, if you had 1000 copies of protein A and only 10 copies of protein B but both proteins had the same mass and charge, mass spectrometry analysis may only pick up the fragments of protein A, meaning you might miss B entirely. To get over these hurdles, Yates introduced a new approach that removed the use of gel electrophoresis to separate proteins.

In the Yates approach, an entire mixture of proteins are broken down to produce a complicated mixture of peptides. The peptides are then separated by a technique called liquid chromatography, which is faster and more sensitive than 2DGE. It also allows peptides to be introduced directly into the mass spectrometer, almost as though they are on a conveyer belt. As each peptide enters the mass spectrometer it identifies its mass and then performs MS/MS on the peptide. Yates and others also developed software tools to automate the process of MS/MS to make it more efficient.

Yates's technique is known as **shotgun proteomics**, and it has been indispensable in allowing scientists to identify and categorize large numbers of proteins from complicated biological samples. Shotgun proteomics significantly expanded the ability to perform large studies of proteins, cells, and tissues, and ultimately helped to establish proteomics as a field.





Ruedi Aebersold

SUBATOMIC COMPONENTS

The building blocks of atoms themselves, such as protons, neutrons, and electrons. The number and ratio of subatomic components in an atom determines its chemical and physical properties as well as its overall identity.

PHYSICAL PROPERTY VS. CHEMICAL PROPERTY

A **physical property** is a quality of a substance that we can observe without changing its identity, such as its colour or its state at room temperature. For example, hydrogen is a colourless gas.

A **chemical property** is a quality of a substance that we can observe in a chemical reaction, which typically alters its identity. For example, hydrogen reacts quickly and aggressively with oxygen gas and produces water.

RUEDI AEBERSOLD: ACCURATELY COUNTING PROTEINS

After you have figured out *which* proteins are in your sample, you still have to figure out *how many* of them there are. Quantifying proteins is especially important for studying the role they play in diseases. For example, a cancerous cell may produce the exact same kind of proteins as a healthy cell, but it may produce 10 times more of a growth protein that makes it toxic.

While MS/MS does tell us how abundant a particular peptide is, the measurement device catches some fragments much more easily than others. This can make it challenging to accurately count all the peptides in a sample. To overcome this, Aebersold made use of a concept from chemistry: **isotopes**. An atom becomes an isotope when there is a change to its number of neutrons—one of its key **subatomic components**. While isotopes act the same way as standard atoms in a chemical reaction, they have slightly different **physical properties** which we can track in mass spectrometry data.

In 1999, Aebersold introduced a technique called Isotope-Coded Affinity Tagging (ICAT), creating chemical tags that could be attached directly to peptides. Aebersold tagged the peptides from a healthy cell with a “light” isotope tag using a standard carbon atom, and he tagged the peptides from a diseased cell with a “heavy” isotope tag using a carbon atom with an extra neutron. He then mixed the samples together and ran them through a shotgun proteomics procedure. The light and heavy peptides are shown to have the same charge, but because of the extra neutron, the peptide from the diseased cell has a slightly higher mass. As a result, the heavier peptide shows up shifted slightly to the right of the light peptide on the mass spectrometry graph.

For the first time, scientists could compare relative quantities of the same proteins in different cells—all thanks to Aebersold’s invention of the isotope tag.

Aebersold also helped overcome some of the limits of shotgun proteomics. He realized that, while it was great for scanning a lot of peptide fragments blindly, sometimes scientists needed a more focused tool. To address this, his lab pioneered **targeted proteomics**. Rather than analyzing millions of peptides fragments, a researcher could program the measurement device of a mass spectrometer to look for a specific set of disease-linked proteins with razor-sharp precision. This breakthrough was so impactful that the journal *Nature Methods* named targeted proteomics its “Method of the Year” in 2012.



Aebbersold's final masterpiece was a targeted strategy called **DIA-SWATH MS**, building on a technique, DIA, which had been proposed by Yates a few years earlier. DIA-SWATH MS allowed scientists to turn a tiny clinical sample like a drop of blood into a permanent digital time capsule representing every measurable protein in the sample. Decades from now, if a scientist discovers a new protein linked to a disease, they don't need a new blood sample—they can just open Aebbersold's digital file and check if that protein was there all along.



Matthias Mann

Nano-ESI made proteomics accessible to virtually all biologists and biochemists, because now they only needed a tiny speck of biological material to run an experiment.

MATTHIAS MANN: DETECTING PROTEINS IN THE SMALLEST BIO-SAMPLES

With Yates solving how to identify proteins, and Aebbersold solving how to count them, the final puzzle piece belonged to Mann. Mann was responsible for making the measurement sensitive enough to work on real biological material. While earlier methods needed large, highly purified samples, Mann's tools brought proteomics down to the scale of a speck of tissue, a drop of blood, and eventually a single cell. These developments allowed proteomics to be used where it counts most: in human biology and medicine.

Mann completed his PhD under John Fenn, the Nobel Prize-winning scientist who invented Electrospray Ionization (ESI). This method is used to turn liquid biomolecules into an airborne gas so the mass spectrometer can analyze them. Mann adapted his mentor's Nobel Prize-winning technique by shrinking it down and developing **nano-electrospray ionization (nano-ESI)**, which allowed the mass spectrometer to analyze microscopic droplets of liquid.

Before Mann, you needed massive, highly purified biological samples to get a reading. With nano-ESI, the machine became so sensitive that it could sequence proteins in femtomole amounts—a scale far below what previous proteomics techniques could reach.

Like Yates and Aebersold, Mann also pioneered a kind of software for proteomics. His was called the “**peptide sequence tag**” approach, which was one of the first computational methods to instantly identify peptides and their chemical modifications directly from tandem mass spectra by matching them against genome databases. Later, his lab created **MaxQuant**, which remains one of the most widely-used software tools for analyzing raw mass spectrometry data today.

Mann then revolutionized quantitative proteomics with a method called **SILAC**. Rather than attaching tags to peptides after harvesting them (like Aebersold’s method), Mann fed the isotope labels directly to living cells in a petri dish, so that the cells built the labels into their own proteins as they grew. This made comparing and quantifying proteins in living cells far simpler. It also enabled a landmark: using SILAC, Mann’s group completed the first analysis of a complete proteome, identifying and quantifying every protein in living yeast cells. This was the first time the full protein complement of any organism had been measured.



Mann’s methods are on the way to be used heavily in biomedicine. If a patient is sick, doctors will take a microscopic slice of tissue or a tiny finger-prick of blood, run it through Mann’s high-speed workflows, and screen their entire proteome in real-time to design personalized medical treatments.

Mann’s lab has also pushed proteomics into intact tissue. In 2022, it introduced Deep Visual Proteomics (DVP), which could extract single cells from a tissue slice and read their full protein content without losing spatial context. DVP has several medicinal applications, whether it is zooming in on cancer cells within otherwise healthy tissue or finding a new use for an existing drug. DVP helped launch spatial proteomics as a field, and Nature Methods named it Method of the Year for 2024—a decade after Aebersold’s targeted proteomics received the same honour.

BUILDING THE FUTURE OF PROTEOMICS

Science rarely moves forward because of a single breakthrough; it progresses when independent findings come together and push us towards new discoveries. John Yates III gave the mass spectrometer the ability to identify proteins, automating how we read a protein's structural fingerprint and organizing peptide fragments with liquid chromatography. Ruedi Aebersold gave the machine the ability to quantify proteins, using isotope chemistry to precisely count fluctuating protein levels and shifting the world of proteomics into an open-access digital era. And Matthias Mann gave the machine the sensitivity to work on real biological material, shrinking the required sample down to microscopic droplets, providing the software tools necessary to map out entire living proteomes, and more recently letting clinicians read a single cell's proteome straight from tissue or blood.

Together, these three pioneers transformed proteomics from a pipe dream into a cornerstone of modern biology, changing how we understand life, health, and disease forever.

Article written by Leanne Cherry

Illustrated by Heather Ng-Cornish

This article has been reviewed by Drs. Ruedi Aebersold, Matthias Mann & John Yates and colleagues for accuracy and accessibility.

MEET THE SCIENTISTS:



Ruedi Aebersold is a Swiss-Canadian scientist and a pioneer in the field of proteomics. He held faculty positions at the University of British Columbia and the University of Washington before co-founding the Institute for Systems Biology in Seattle. In 2004, he joined ETH Zürich, where he established the Institute of Molecular Systems Biology. His research group developed widely used technologies, software and statistical tools for studying the proteome, helping make proteomic research more accurate, reproducible and accessible. His work has received numerous international honours, including the Marcel Benoist Swiss Science Prize and the 2024 Heineken Prize for Biochemistry and Biophysics.

Matthias Mann is a pioneer in mass spectrometry-based proteomics. He studied physics and mathematics at Göttingen University and completed his Ph.D. at Yale University, where his work contributed to the development of electrospray ionization for large biomolecules. Throughout his career, he has developed foundational technologies and computational methods for identifying and measuring proteins, including approaches now widely used in proteomics research. Since 2005, he has led the Department of Proteomics and Signal Transduction at the Max Planck Institute of Biochemistry in Munich. His many international honours include the Leibniz Prize, Louis-Jeantet Prize for Medicine and 2024 Heineken Prize for Biochemistry and Biophysics.



John R. Yates III is a pioneer in mass spectrometry-based proteomics and a professor at Scripps Research. He earned his Ph.D. in Chemistry at the University of Virginia, where he studied protein sequencing using tandem mass spectrometry, before completing postdoctoral training at Caltech. Yates is the lead inventor of SEQUEST, software that helps identify proteins by matching mass spectrometry data with sequences in protein databases, and a principal developer of shotgun proteomics for analyzing complex protein mixtures. His laboratory continues to develop proteomic technologies for investigating proteins and biological systems. His work has been recognized with numerous international awards in analytical chemistry and proteomics.

We wish to thank Profs. Aebersold, Mann, and Yates and their collaborators for their input in this article.



YOUTH ACCESSIBILITY REVIEW

This article was reviewed by high school students through the Canadian Association for Girls in Science (CAGIS)—Canada’s largest and longest-running STEM (science, technology, trades, engineering, and math) club for girls and gender-diverse youth aged 7-17. This award-winning club, founded in 1992, supports interest in STEM with virtual programming and local clubs that visit labs, workshops, and field sites to meet mentors and do fun, hands-on activities. Their thoughtful feedback on clarity, accessibility, and reader engagement helped shape the final version of this article and ensure it is engaging and accessible for youth readers.



Arshia Nair • Grade 11

“I am interested in the science of neurodegenerative diseases, which fuels my desire to pursue a career in healthcare.”



Cynthia Rayson • Grade 11

“I hope to study biomedical engineering and develop new dental technologies to enhance patient care.”



Valini Parasram • Grade 12

“In the future I hope to study chemistry and its nuclear applications.”



June Liu • Grade 12

“I aspire to pursue a career in healthcare or biomedicine with a focus on applied research and potentially business, re-imagining the way we approach real world issues with practical and innovative solutions.”



ZOOMING IN ON BIOLOGICAL MOLECULES: A NEW PERSPECTIVE

DR. WOLFGANG BAUMEISTER

CANADA GAIRDNER INTERNATIONAL AWARD WINNER

Director Emeritus and Scientific Member, Max-Planck-Institute of Biochemistry, Martinsried, Germany; Distinguished Professor, ShanghaiTech University, China

SUMMARY

Wolfgang Baumeister developed a technology called cryo-electron tomography which allows researchers to see the 3D structure of the inside of a cell. This method involves flash-freezing cells when they are active and using a beam of electrons like a camera to capture the cell from multiple angles. The result is a detailed 3D image that reveals how molecules interact and come together to form the cell's inner machinery. Traditionally, scientists studied just one part of a cell at a time. Baumeister's technology allows researchers to see how these parts fit together, giving us a much clearer picture of how cells are organized and function.

STUDENT REVIEWERS:



ADRIENNE
Grade 12



DEEPA
Grade 12



RANEEM
First year
university



VIENNA
First year
university

Cells are the foundation of life on Earth. Despite their microscopic size, they are incredibly complex living systems which depend on numerous internal components to function. We have been exploring how cells are built since the late 1800s, and this work continues today within the field of structural biology.

A cell's structure can reveal key information about its role in disease or how we could use it to improve our medications. However, structural biologists face a major challenge: most cells are so small that they are invisible to the naked eye. To overcome this, we have had to develop highly innovative imaging techniques.

For Dr. Wolfgang Baumeister, a scientist at the *Max Planck Institute of Biochemistry*, his greatest achievement was developing a groundbreaking new imaging technique called **cryo-electron tomography (cryo-ET)**.

This method allows us to generate clear and accurate 3D models of cells and their components in their natural state. Baumeister's advancements have established cryo-ET as an essential tool in structural biology. His work enables us not only to visualize a cell's individual components, but also to paint a picture of how these components come together and form a living being. Altogether, Baumeister has provided crucial insight into the structure of the most fundamental unit of life.

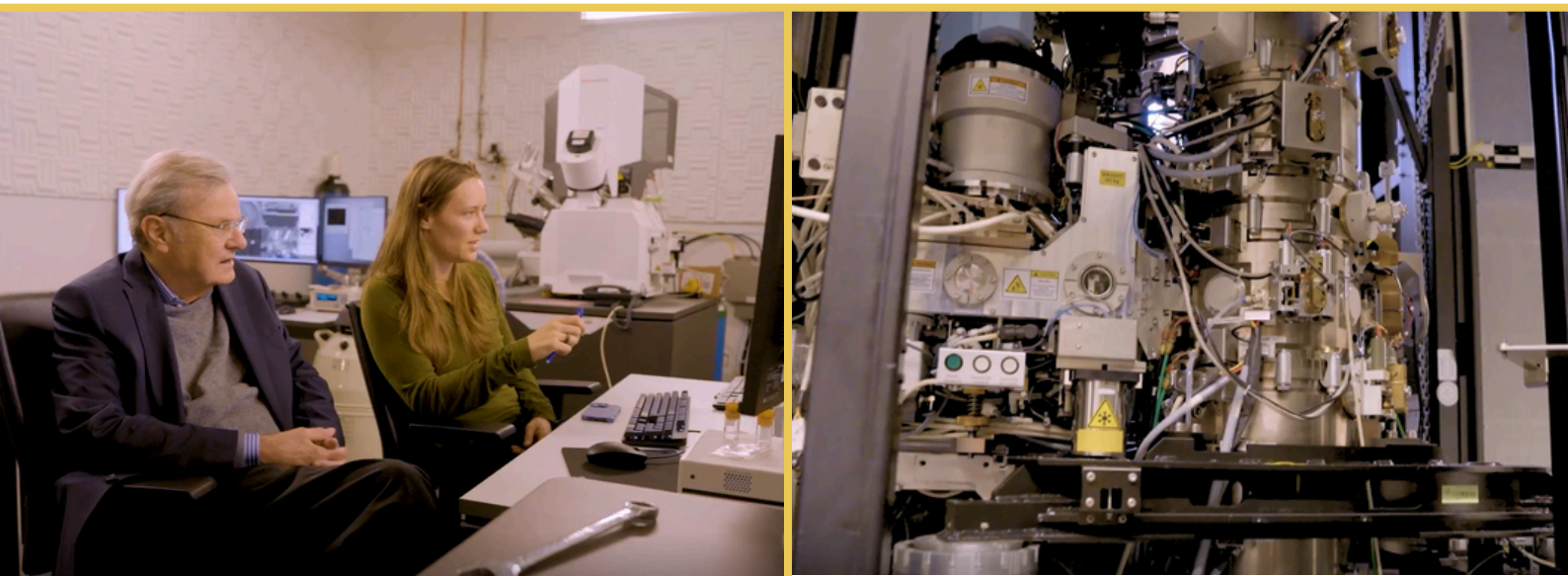
A BRIEF HISTORY OF BIOMOLECULE IMAGING

For most of structural biology's history, we used a technique called **X-ray crystallography** to visualize proteins and other small biological molecules. This technique works by creating millions of copies of a particular protein and arranging them into a crystalline structure—a repeating, symmetric arrangement of molecules which forms a solid crystal. We then direct X-rays at the crystal, and as the rays pass through it, they scatter in different directions depending on the protein's structure. By analyzing these scattering patterns, we can reconstruct a 3D model of the individual protein.

Like any laboratory technique, X-ray crystallography has its limits. Generally speaking, X-rays can only be used to visualize proteins when the proteins are arranged into a larger structure such as a crystal. An individual protein molecule usually cannot scatter the X-rays enough to create a pattern that we can interpret. One of the major problems with X-ray crystallography is that not every biological molecule can readily form a crystal. Determining which proteins can form crystals, along with creating the ideal conditions for the crystallization process, is incredibly difficult.

Moreover, even for proteins that crystallize easily, X-ray crystallography requires that we obtain a highly purified sample, one which contains millions of copies of the protein we want to image. This is to ensure that the resulting protein crystal produces a scattering pattern which accurately reflects the protein's structure. Many purification techniques change the structure or composition of a molecule, and this puts us at risk of losing crucial information during our experiments.

After working with X-ray crystallography for many years, Baumeister became well-acquainted with these challenges. He began to think about new ways of approaching structural biology problems—as did other scientists in the field.



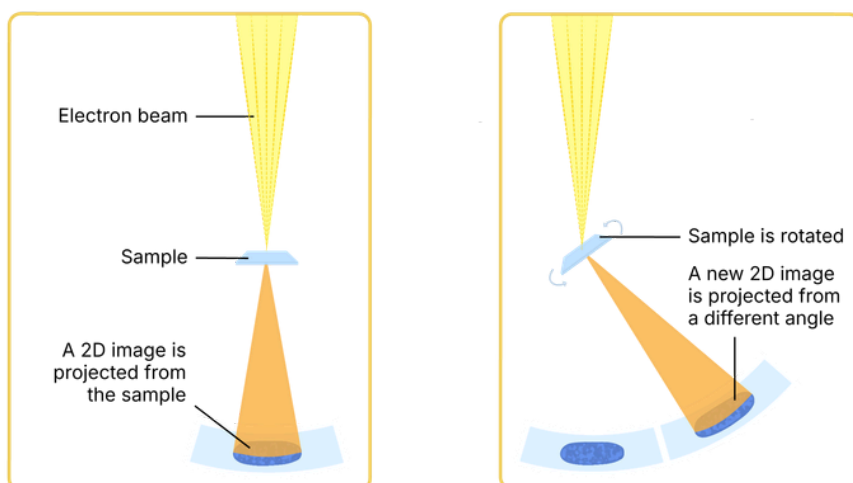
INTRODUCING CRYO-ET

In the 1970s, scientists developed cryo-electron microscopy (cryo-EM), a breakthrough imaging technique that earned the 2017 Nobel Prize in Chemistry. Baumeister later built on this technology by developing **cryo-electron tomography (cryo-ET)**, which allowed us to create detailed 3D images of cells.

Rather than using X-rays, cryo-ET directs a beam of electrons at a biological sample, such as a cell or one of its many components. Electron beams are much higher in energy than X-rays, and as a result they can image a molecule's structure with greater precision and accuracy. However, the higher energy also makes the beam more likely to cause **radiation damage** to the sample.

To keep the cells hydrated and to minimize the damage, we plunge the sample into a liquid cooled to about -180°C . When water freezes, its molecules typically rearrange into a rigid, crystalline structure. This is how liquid water becomes solid blocks of ice. However, the method used in cryo-ET freezes our sample via a different process called vitrification, which solidifies our sample's molecules in place without allowing rigid ice crystals to form. By preventing the molecules from rearranging into ice crystals, the sample is essentially frozen in time, meaning we can observe it while it is close to its natural state. The vitrification process also protects the sample from the energy of the electron beam.

When the electrons pass through the biological sample, they leave a shadow that reflects the sample's internal and external structure (**Figure 1**). We rotate the sample several times so that we can send electrons through it from many different angles. Each shadow that the high-energy beam leaves behind shows us the sample's molecular structure from a slightly different perspective, just as though we were photographing an object from multiple positions (**Figure 2**). From there we can compile the images and compute a 3D model of our sample (**Figure 3**).



RADIATION DAMAGE

The process by which high-energy waves or particles affect the atoms of a physical object, including living and non-living things. High energy beams can break chemical bonds, and in the context of structural biology, they can destroy our sample.

FIGURE 1

An electron beam passes through the sample which projects a two-dimensional image of a cell.

FIGURE 2

The sample is rotated, allowing the electron beam to project an image of the cell from a different angle.

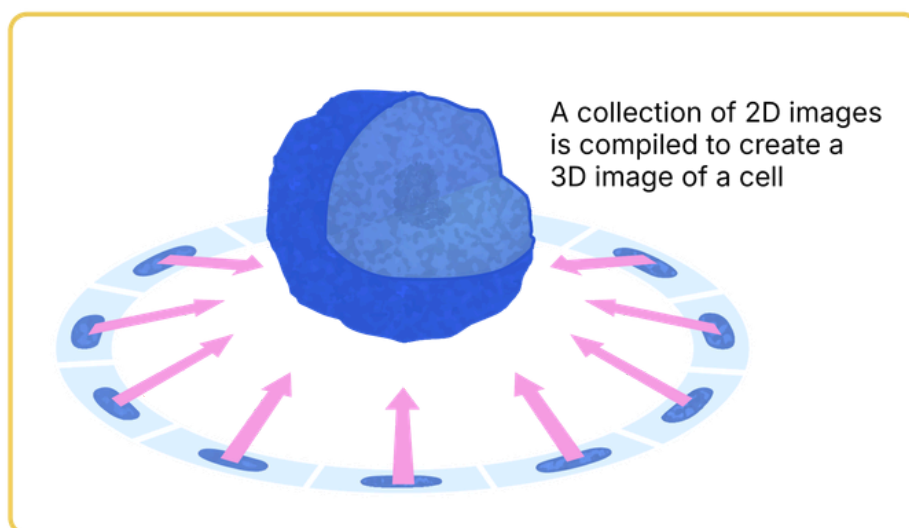


FIGURE 3
Many two-dimensional images are taken of the cell. This collection is used to create a three-dimensional representation of the cell.

ADVANTAGES OF CRYO-ET

Baumeister's technique provided several important advantages over earlier methods of imaging cells. Like X-ray crystallography, the original cryo-EM methodology also suffered from needing incredibly pure samples of a biological molecule, as it needed many copies of the same molecule frozen in different orientations to render a 3D model.

Cryo-ET is a different story. Because we rotate the sample to capture it from different angles, this technique only requires a single copy of the sample to visualize its 3D structure. As a result, we are not limited to molecules that need to form a crystalline structure to be seen or undergo a harsh purification process. We can therefore use cryo-ET to uncover the structure of whole, individual cells—along with all of their internal components—while they are still in their native state.

Previously, we approached structural biology problems by isolating individual components of a cell and trying to capture what they looked like. With cryo-ET, we can observe a cell in its near-natural environment, allowing us to produce a much more accurate model of its structure and gain insight into how it functions.

DEVELOPING CRYO-ET

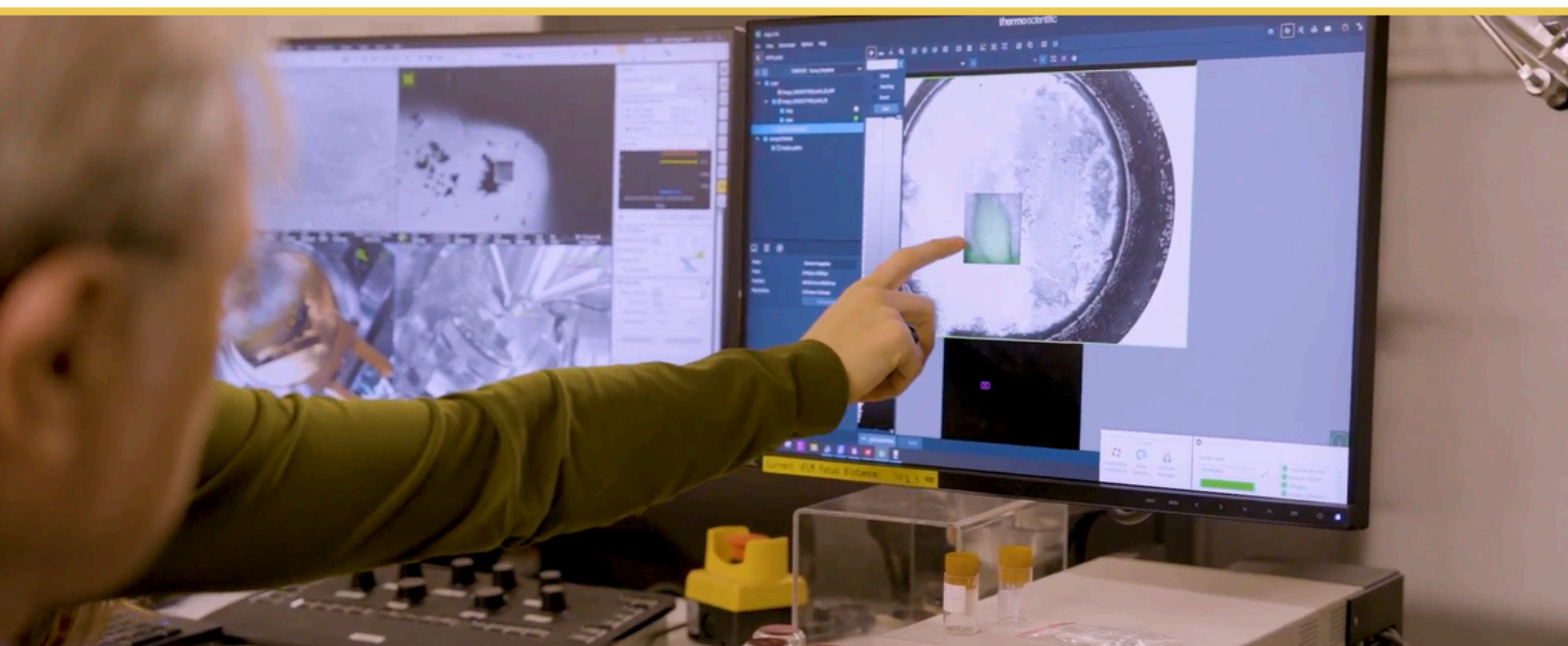
While cryo-ET is incredibly powerful today, it would never have gotten to where it is now without Baumeister's career-long devotion to its advancement. He had to overcome hurdle after hurdle, not only to refine the technology, but to prove that it could be used to solve structural biology problems in the first place.

Electron microscopy—the technique that first enabled us to image tiny structures using a beam of electrons—was initially designed to be operated and adjusted manually. With the help of a computer, we would position the sample, focus the electron beam, and shoot the sample to capture a 2D image. However, cryo-ET, which also uses an electron beam, requires the sample to be shot from around 100 different angles. At one point, this meant we had to manually reposition and recentre the biological sample before every image. This process was not only time-consuming, but also increased the risk of introducing errors and causing radiation damage.

Knowing the limitations of manual cryo-ET, Baumeister developed software and hardware that helped to automate this process. He also developed technology to help keep the electron dose within tolerable limits, thereby minimizing radiation damage.

Even after making the technique easier to use, Baumeister still had to demonstrate just how useful cryo-ET could be. The vitrification technique used in cryo-ET today was first used for the Nobel-Prize-winning cryo-EM. On his quest to demonstrate cryo-ET's utility, Baumeister used cryo-EM's solidification technique to image *Dictyostelium*—a tiny, single-celled organism. *Dictyostelium* cells are incredibly thin, making them ideal for cryo-ET trials because electrons can pass through them without much trouble. Baumeister's work with this organism proved definitively that cryo-ET could visualize the internal structure of cells, all the way down to the scale of five nanometres—which is over ten thousand times smaller than a human hair.

Baumeister's work also greatly increased the range of cells we could examine using cryo-ET. As mentioned, cryo-ET is best suited for thinner samples. However, many of the cells that we are interested in, such as human cells, are too thick to be put through a cryo-ET procedure in their native state. To overcome this hurdle, Baumeister adapted an existing technology called **focused ion beams (FIBs)** to help make cells thinner. Essentially, FIBs allow us to make razor-thin slices of a biological sample directly out of tissues and organisms. We can then use cryo-ET on each of the tissue slices to render a 3D model of the tissue's structure. Baumeister's innovative use of FIBs gave us the opportunity to image practically any biological sample we could think of; the possibilities became endless.



The algorithm provides so much clarity that it can identify individual structures found within the cell which carry-out essential cellular functions.

Additionally, Baumeister and his team created a computer algorithm that helps clarify the images taken during a cryo-ET procedure. Because cells are so complex and densely organized, cryo-ET images can look very busy when they are first taken. Moreover, while the electron beam is essential for capturing images, it can also introduce noise and irregularities into our images, making image processing even more difficult. Baumeister thus created a **denoising algorithm for cryo-ET**, which was the first of its kind to both remove the unnecessary information added by the electron beams and preserve structural information of the cell.

BAUMEISTER'S OWN DISCOVERIES USING CRYO-ET

Beyond all of the work that he did to improve cryo-ET as a technology, Baumeister made many important structural biology discoveries through his own use of the technique. The bulk of his research focused on the **proteasome**—the structure within cells responsible for breaking down damaged or faulty proteins.

Over the course of his career, Baumeister has revealed much of the proteasome's structure, beginning with a few particles and eventually rendering the whole thing. Proteasome malfunction is thought to play a role in many diseases such as Alzheimer's and Parkinson's, and understanding how the proteasome is built can help us figure out how to help it when it stops working. Since his work on the proteasome, he has gone on to image several other important molecular machines within cells.

Baumeister's dedication and contributions to the field of structural biology cannot be overstated. Thanks to his career's worth of effort to pioneer, refine, and apply cryo-ET, Baumeister has given us a glimpse into the structure of life itself.

Article written by Leanne Cherry

Illustrated by Heather Ng-Cornish

This article has been reviewed by Dr. Wolfgang Baumeister and colleagues for accuracy and accessibility.



MEET THE SCIENTIST: Dr. Wolfgang Baumeister

Wolfgang Baumeister is a German biophysicist and a pioneer in structural biology. He studied biology, chemistry and physics and earned his Ph.D. in Biophysics from the University of Düsseldorf. In 1982, he joined the Max Planck Institute of Biochemistry, where he later became Director of the Department of Structural Biology. Baumeister and his team have developed and advanced electron microscopy techniques that allow scientists to study the molecular structures inside cells in remarkable detail. His work has transformed how researchers investigate the organization and function of cells. His many international honours include the Louis-Jeantet Prize for Medicine and the 2025 Shaw Prize in Life Science and Medicine.



YOUTH ACCESSIBILITY REVIEW

This article was reviewed by high school students through the Canadian Association for Girls in Science (CAGIS)—Canada's largest and longest-running STEM (science, technology, trades, engineering, and math) club for girls and gender-diverse youth aged 7-17. This award-winning club, founded in 1992, supports interest in STEM with virtual programming and local clubs that visit labs, workshops, and field sites to meet mentors and do fun, hands-on activities. Their thoughtful feedback on clarity, accessibility, and reader engagement helped shape the final version of this article and ensure it is engaging and accessible for youth readers.



Adrienne Ma • Grade 12

"I hope to pursue a career in optometry to combine my love for helping others and my fascination for the human eye."



Deepa Kalia • Grade 12

"I hope to combine my love of technology with my passion for business and explore how technology can be used to create innovative solutions and opportunities."



Raneem Salah • First-year university

"I'm excited to study human biology and find ways to impact society using that knowledge!"



Vienna Cipparrone • First-year university

"I am intending on studying neuroscience and psychology, and I want to explore how psychological disorders affect brain structure and function."



FROM DISCOVERY TO DISTRIBUTION: BRINGING THE ORAL CHOLERA VACCINE TO THE WORLD

PETER GILGAN CANADA GAIRDNER GLOBAL HEALTH AWARD WINNERS

Prof. John D. Clemens

Senior Scientific Advisor to the Director General, International Vaccine Institute, Seoul, South Korea; Adjunct Professor of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, United States

Dr. Jan Holmgren

Senior Professor, Sahlgrenska Academy, University of Gothenburg, Sweden

SUMMARY

Over the past 40 years, Drs. John D. Clemens and Jan Holmgren have worked together to develop the only oral cholera vaccines approved by the World Health Organization (WHO). Cholera is a bacterial disease that causes diarrhea and is often spread through contaminated water. If not treated quickly, cholera can be deadly, particularly in lower income countries where access to clean and safe water may be limited. Throughout their careers, Clemens and Holmgren have devoted themselves to developing and distributing oral cholera vaccines. They have also carried out large studies to demonstrate how well the vaccines work. Their work has saved countless lives and has fundamentally changed how global health organizations respond to cholera.

STUDENT REVIEWERS:



CELINE
Grade 10



HARGUN
Grade 10



RHYTHM
Grade 8



ROSE
Grade 9

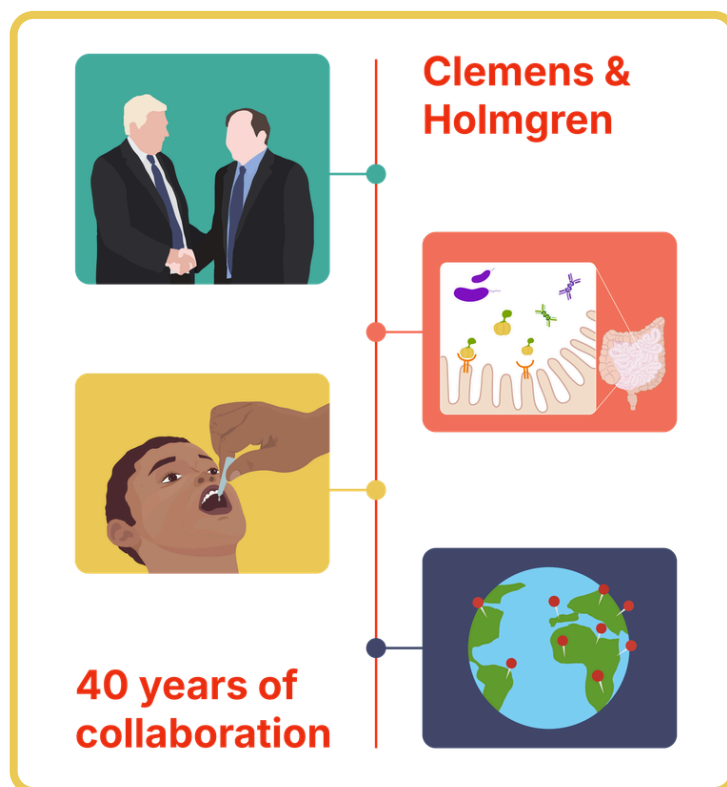
When we hear about major scientific achievements, we sometimes forget about the years of research and hard work that a team has to endure before reaching a breakthrough. Drs. John D. Clemens and Jan Holmgren remind us that continuous effort and perseverance in science can have extraordinary payoff for everyone involved. After four decades of research and collaboration, these researchers have given the world safe, inexpensive, and effective oral vaccines against cholera.

Cholera is a bacterial infection that causes severe diarrhea and vomiting after ingesting contaminated water. It can lead to life-threatening dehydration, especially in children, if it is not treated quickly. Thanks to functional **sanitation systems**, the bacteria that cause cholera, *Vibrio cholerae*, has been nearly eradicated in developed countries.

However, in developing parts of the world, where many people lack reliable access to clean water and healthcare services, cholera continues to pose a serious public health challenge. Outbreaks are especially common during periods of war and environmental crises, such as floods and cyclones, that disrupt water and sanitation systems.

Clemens and Holmgren have long understood the severity of cholera and have dedicated a significant portion of their careers to developing, distributing, and studying the impacts of **oral cholera vaccines (OCVs)**. John Clemens is an **epidemiologist** while Jan Holmgren is an **immunologist**; together, the pair was uniquely positioned to take on a disease such as cholera that affects health on a global scale.

As Clemens said in an interview, “My clinical and epidemiological skills and Jan’s basic science discovery skills formed a perfect partnership that has really sustained the work that we have done over the past four decades.”



But their work has not been easy. These researchers have run into obstacles at just about every step of the process, from the initial development of OCVs to their efforts to distribute the vaccine to communities that need it most. It was only in the past decade that OCVs were universally recognized as an essential tool for managing cholera; without Clemens and Holmgren’s perseverance, we might never have gotten the life-saving vaccines we have today (Figure 1).

SANITATION SYSTEM

A region's facilities for producing safe, clean drinking water and maintaining and disposing of human waste

EPIDEMIOLOGIST

Someone who studies health and disease at the population level

IMMUNOLOGIST

Someone who studies the human body's immune defenses

FIGURE 1

Over the course of 40 years, Clemens and Holmgren's partnership has led to remarkable global health outcomes. From discovering the body's defense mechanism against cholera, to developing an oral vaccine that harnessed that discovery, these milestones are the culmination of long-term collaboration.

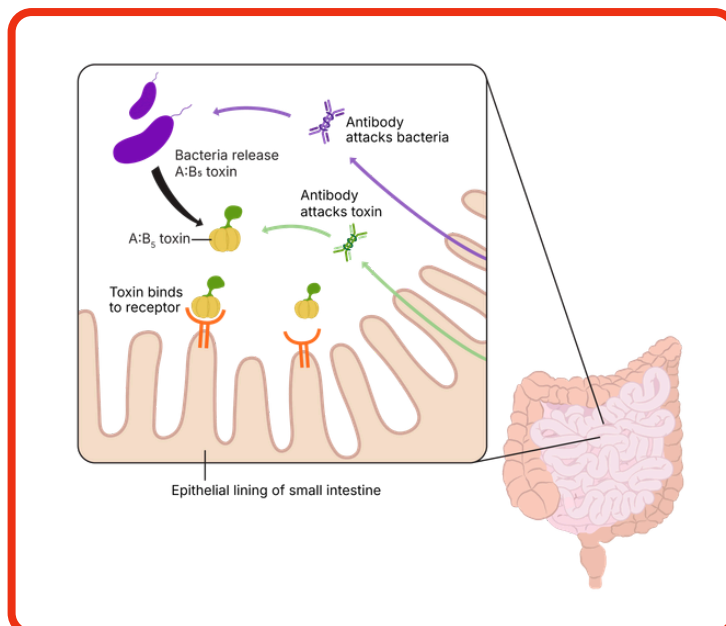
CREATING DUKORAL™, THE FIRST WHO-PREQUALIFIED OCV

In the 1960s, cholera was quickly tearing its way through Asia, despite the availability of an injectable cholera vaccine that had been in use for over 70 years. Studies conducted across thousands of people showed that this injectable vaccine only provided short-term protection lasting three to six months—and even then, they only reduced cholera cases by only about 50 percent. By the 1970s, the World Health Organization (WHO) had stopped recommending injectable cholera vaccines and new alternatives were being explored.

To develop a more effective vaccine, scientists first needed a better understanding of how cholera causes disease. Holmgren and his team in Sweden studied *Vibrio cholerae* bacteria, identifying the structure and function of the toxin it produces, which is responsible for the disease's most serious symptoms: severe diarrhea and dehydration.

Their research shed light on the toxin's structure, showing that it has five cell-binding (B) pieces connected to a toxic, active (A) piece. This led to it being named the **A:B₅ toxin**. They also identified the **receptor** in the human intestine that B pieces bind to, which has a lock-and-key kind of mechanism. When the five B pieces (the key) attach to the receptor (the lock), the toxic A piece is taken up by the body and released into the cells, allowing it to become active and make us sick with symptoms like vomiting and diarrhea.

The team also discovered that the body's primary defense mechanisms against cholera—namely, proteins called **antibodies**—are made by the local **immune system** within the intestine itself (**Figure 2**). These discoveries collectively paved the way for developing a new vaccine.



RECEPTOR

A protein that receives a signal (often a chemical message like a hormone) and produces a response, often found within biological systems. In the case of the cholera toxin, it binds to a receptor in the intestine and makes us sick

ANTIBODY

A protein made by our immune system to fight bacteria and viruses. Cholera antibodies are specifically produced in the intestine, but antibodies for diseases more broadly can be produced in many different locations around the body

IMMUNE SYSTEM

The body's network for defending against germs like viruses and bacteria

FIGURE 2

Within the small intestine, cholera bacteria release A:B₅ toxins. The toxins bind to receptors that are attached to the epithelial lining of the small intestine. Antibodies are produced below the epithelial lining. Some anti-bodies attack the toxin, while other anti-bodies attack the bacteria directly.

Earlier injectable vaccines used a **killed whole-cell approach**, containing inactivated (killed) copies of *Vibrio cholerae*. After you get vaccinated, your immune system recognizes the bacteria and begins creating antibodies against it. If you contract a live cholera infection after your vaccination, your immune system will be more prepared to defend against it, because it will have made the cholera antibodies before.

Many of the life-saving vaccines that we rely on today use inactivated versions of a disease to help us create antibodies. A problem with the injectable cholera vaccine, however, was that it only stimulated antibody production in the blood, rather than in the intestine where cholera bacteria are most prominent.

Holmgren and his team thus proposed a vaccine that could be taken by mouth. They showed both in animals and humans that the body produced significantly more intestinal antibodies when the vaccine was administered orally rather than by injection. The team also proposed that the vaccine contain killed whole-cells and an inactivated form of the toxin to help the immune system fight back against both the cholera bacteria and the toxin they produce at the same time. These developments led to the production of the first oral cholera vaccine, **Dukoral™**.

Clemens and Holmgren began collaborating in 1985 to run a large-scale trial in Bangladesh on Dukoral™'s efficacy. The trial evaluated two versions of the vaccine: one containing both the B-subunit and killed whole cells (BS-WC OCV), and another containing only killed whole cells (WC-only OCV). With over 90,000 volunteer participants in the trial, both versions of Dukoral™ proved to be effective, giving participants 50-60 percent protection over three years after receiving a dose. Dukoral™ then became the first OCV to receive WHO pre-qualification, a designation confirming global standards for quality, safety, and efficacy.



FIGURE 3

A single conversation can change the course of a career. In 1970, shortly after completing his PhD, Jan Holmgren (right) was encouraged by his department head, Örjan Ouchterlony (left), to turn his research to cholera. With the seventh cholera pandemic spreading and existing vaccines proving ineffective, Holmgren was inspired to help develop a better one. That moment set him on a path that would define his career.

PRODUCING AN OCV LOCALLY IN VIETNAM

Vietnam was one of the many countries in Asia suffering from cholera outbreaks in the 1960s and '70s. When the successful results from the Bangladesh trial were released in the late 1980s, a Vietnamese professor reached out to Holmgren and Clemens about producing and testing a local version of the WC-only OCV which was less expensive than the BS-WC OCV. Holmgren helped transfer the WC-only vaccine production technology to Vietnam, and Clemens helped to conduct additional large-scale trials to assess its effectiveness. These studies found that the vaccine provided protection for approximately three to five years. Since the 1990s, more than 11 million doses of the locally produced vaccines, ORC-Vax/mOrcVax™, have been administered, contributing significantly to Vietnam's successful control of cholera.

While mORC-Vax™ was incredibly useful in its own right, it was not without its limitations. Vietnam's National Regulatory Agency (NRA) was not approved by WHO, and as a result, it was not eligible to be authorized for use outside of the country. Furthermore, Dukoral™ was regarded as too expensive for public health use at this point. For Clemens and Holmgren, this challenge marked the beginning of the next stage of their work: finding a way to make oral cholera vaccines available on a global scale.



FIGURE 4

Jan Holmgren (far left) and John Clemens (far right) pictured with colleagues in Vietnam.

OVERCOMING LIMITATIONS BY DEVELOPING SHANCHOL™ OCV

In 1999, Clemens had become the director of the International Vaccine Institute (IVI). He and Holmgren continued their work together on OCVs, modifying the composition of ORC-Vax™ and transferring production over to Shantha Biotechnics, an Indian company that was approved by WHO. They ran yet another large field trial, and found that the India-produced OCV named Shanchol™ could confer 60 percent protection for at least five years. By 2009, Shanchol™—costing only \$1.85 USD per dose—received WHO prequalification, enabling it to be used globally.

Despite these successes, some leading global health organizations remained unconvinced that OCVs were effective enough to play a major role in cholera control. They were worried that OCVs might discourage local governments from investing in better water and sanitation infrastructure; poorly built and mismanaged sewer systems are a large reason cholera can be transmitted so quickly in the first place. Before OCVs like Shanchol™ could be distributed to the rest of the world, Clemens and Holmgren needed to prove to the global health community that large-scale distribution would be worth it.

To address these concerns, Clemens and Holmgren launched a large multi-country study called DOMI—their largest project yet. While their previous trials looked at vaccine efficacy, DOMI focused more on the logistical aspects of global vaccine distribution. The project examined several key questions, including whether there was sufficient demand for OCVs, whether large-scale distribution was feasible, and whether vaccination programs could reduce the health and economic burden of cholera in a cost-effective way. Finding answers to these questions would be essential to show policymakers how necessary OCVs were.

One of the study's most important findings was that OCVs not only protected vaccinated individuals, but also indirectly protected unvaccinated members of the community. This was due to a phenomenon known as herd immunity—when enough people are vaccinated against a disease that it limits spread even to the unvaccinated. The ability of OCVs to provide herd immunity also suggested that they would be cost-effective to distribute by reducing the overall number of cholera cases, and thus the economic burden of disease. Clemens and Holmgren compiled this evidence into a comprehensive report, making the case to WHO that OCVs were essential in global cholera control efforts.

THE FINAL OUTCOME

Clemens' and Holmgren's paper was transformative for global health policy on cholera. Released during a devastating cholera epidemic in Haiti, it reinforced the growing recognition that OCVs were an important tool for controlling outbreaks. In 2011, the WHO recommended all countries already having or being under immediate threat to get cholera to use Shanchol™ or Dukoral™ OCVs in their cholera control programs. By 2013 Shanchol™ was being purchased and used for the global stockpile of OCVs. Clemens' and Holmgren's work was also important for the development of WHO's initiative, "Ending Cholera: A Global Roadmap to 2030," which began back in 2017. The initiative aims to largely eliminate cholera deaths and cholera transmission by 2030.

Today, more than 100 million doses of OCVs developed through Clemens and Holmgren's work have been administered worldwide. These vaccines are now a central part of global cholera control efforts and are routinely deployed in response to outbreaks and humanitarian emergencies. Thanks to four decades of laboratory research, clinical trials, and international collaboration, OCVs have been empowered to protect vulnerable communities around the world.

Article written by Leanne Cherry

Illustrated by Heather Ng-Cornish

This article has been reviewed by Drs. John Clemens and Jan Holmgren and colleagues for accuracy and accessibility.

MEET THE SCIENTISTS:



John Clemens is an infectious disease epidemiologist whose research has focused on developing and evaluating vaccines in populations affected by infectious diseases. A graduate of Stanford University and Yale University, he led the first efficacy trial of an oral cholera vaccine at icddr,b in Bangladesh. He later became the first Director-General of the International Vaccine Institute, where he led the team that developed Shanchol, an oral cholera vaccine that became an important tool for global cholera prevention. Clemens has also held leadership positions at UCLA and icddr,b and currently serves as Senior Scientific Advisor to the Director-General of the International Vaccine Institute.



Jan Holmgren is a physician-scientist and Senior Professor at the University of Gothenburg in Sweden. His research has advanced our understanding of cholera, mucosal immunity and vaccination. Holmgren and his colleagues helped uncover how cholera toxin interacts with human cells and identified important immune mechanisms that protect against the disease. This research contributed to the development of Dukoral, the first effective oral cholera vaccine, and helped enable the development and production of additional oral cholera vaccines around the world. His work has had a major impact on the prevention of cholera and the development of vaccines that stimulate protective immune responses at mucosal surfaces.



YOUTH ACCESSIBILITY REVIEW

This article was reviewed by high school students through the Canadian Association for Girls in Science (CAGIS)—Canada’s largest and longest-running STEM (science, technology, trades, engineering, and math) club for girls and gender-diverse youth aged 7-17. This award-winning club, founded in 1992, supports interest in STEM with virtual programming and local clubs that visit labs, workshops, and field sites to meet mentors and do fun, hands-on activities. Their thoughtful feedback on clarity, accessibility, and reader engagement helped shape the final version of this article and ensure it is engaging and accessible for youth readers.



Rhythm Sehgal • Grade 8

“I hope to study Health Science and Genomics to make new discoveries in healthcare.”



Rose Isakson • Grade 9

“I hope to study biology, particularly animal behaviour.”



Celine C.A. Chen • Grade 10

“I hope to study biomedical informatics and enjoy learning about how technology can improve healthcare.”



Hargun Kaur • Grade 10

“I’m interested in environmental science and how STEM can help create a more sustainable future.”

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