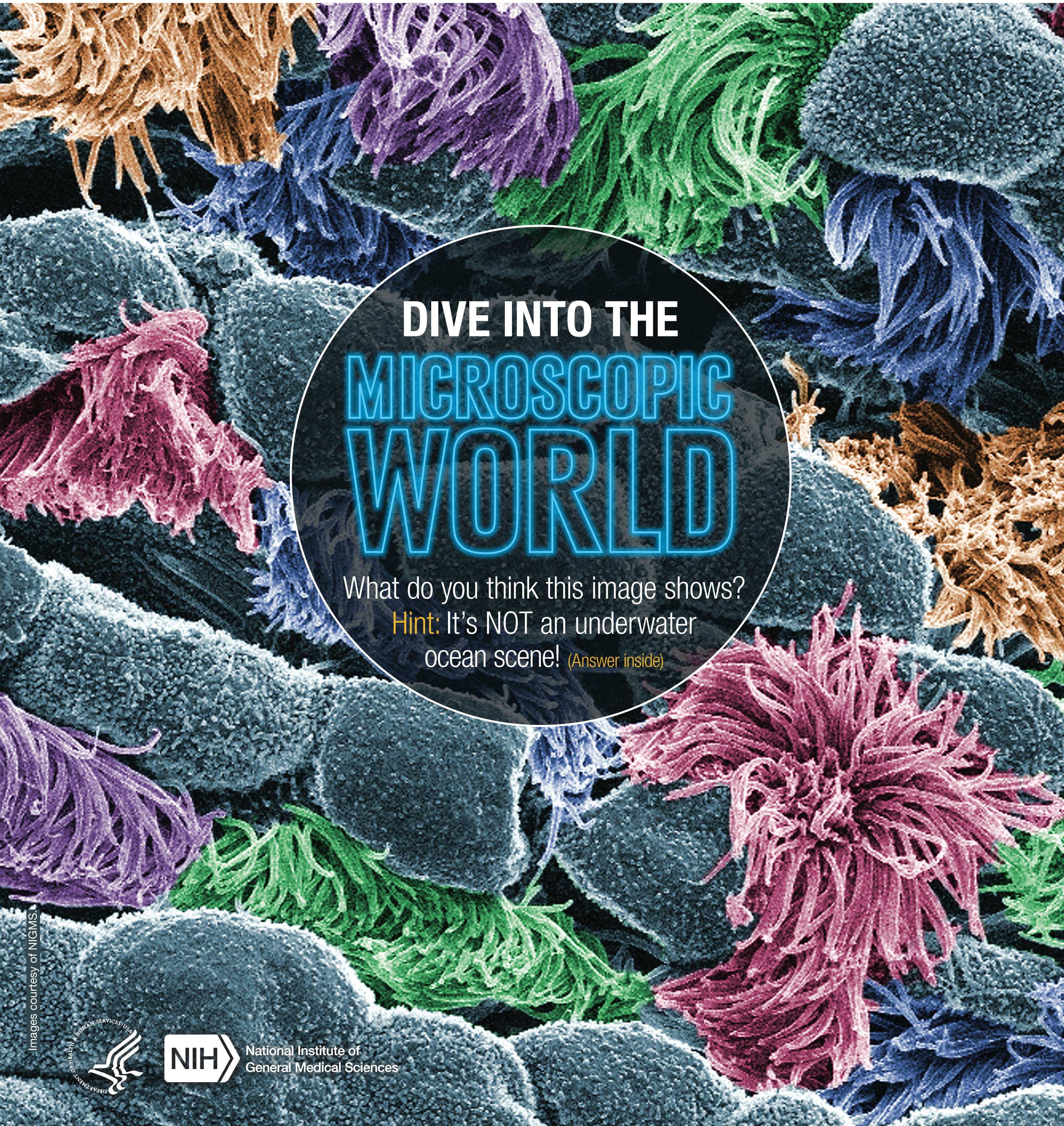
nigms.nih.gov/education/pathways

The Imaging Issue

PATHWAYS



DIVE INTO THE MICROSCOPIC WORLD

What do you think this image shows?
Hint: It's NOT an underwater ocean scene! (Answer inside)

Images courtesy of NIGMS.

NIH National Institute of General Medical Sciences

THE MAJESTIC MICROSCOPIC WORLD

Discover how scientists unlock the big (or very small!) mysteries of our cells and molecules.

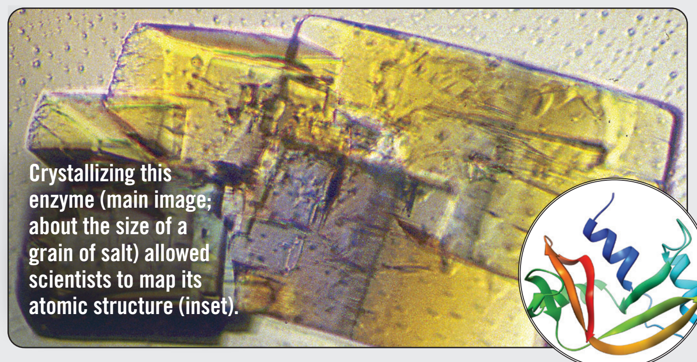
Imagine you re trying to take a photo of something small say, a bug with a cool pattern on its back. You zoom in, but the image gets grainy and blurry.

Bugs can get pretty tiny, but they re huge compared to your cells, let alone your atoms. About 5 million hydrogen atoms can fit on the head of a pin. How can something so astonishingly small be photographed?

Over the past century, scientists have developed a variety of ingenious technologies to answer this question. Using increasingly advanced imaging tools, scientists have peered at protein molecules folded like origami, cells pushing out harmful particles, and much more. (Check out some examples featured on these pages!) Studying the body s normal and abnormal processes can lead to developing more effective, targeted treatments.

How do you digest food?

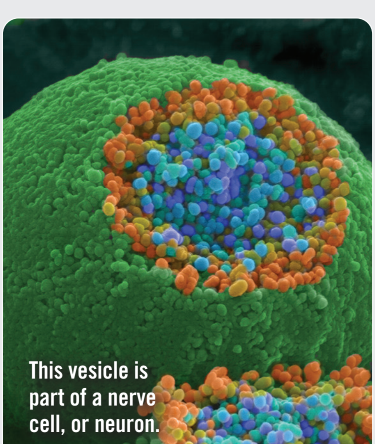
Cool image fact The protein ribonuclease A is found in all living cells. It is an enzyme that breaks down the RNA found in foods like meat and legumes, helping with digestion.



Crystallizing this enzyme (main image; about the size of a grain of salt) allowed scientists to map its atomic structure (inset).

How scientists created these images Using chemistry, scientists prompted the protein sample to grow into a highly organized form called a crystal (over months). Then they fired X-rays through it. The X-rays bent in different directions upon hitting the individual atoms in the protein crystal, forming a dot pattern. Scientists used a formula to infer what 3D structure would cause that pattern. This process, **X-ray crystallography**, only works with specimens that *can* be crystallized.

How does your brain send messages?



This vesicle is part of a nerve cell, or neuron.

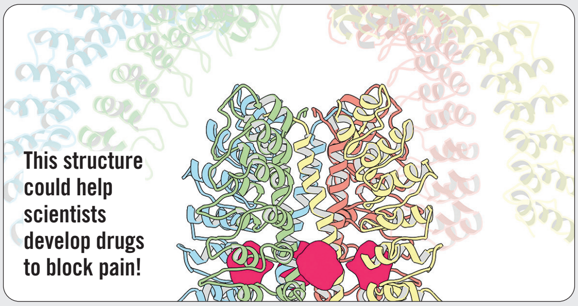
Cool image fact This nerve ending has been broken open to reveal *vesicles* containing chemicals called *neurotransmitters* that pass messages in the nervous system. Researchers colorized the vesicles in orange and blue to help viewers see the different parts of the image.

How scientists created this image A **scanning electron microscope** works by moving (scanning) a narrow beam of electrons across a sample (which is often coated in gold to make it conductive). By detecting how electrons are reflected or absorbed, scientists can create an image. But why not just shine a light? Light is made up of photon particles that reflect off objects and into our eyes. But some specimens are too tiny for a photon's wavelength! Electrons have a smaller wavelength that can interact with tiny specimens, such as the one pictured here.

ON THE COVER

Magnify a throat 10,000x and you'd find a "sea" of mop-like cells that sweep out unwanted particles with a continuous motion, as shown in this colorized mouse throat.

How do you sense pain?

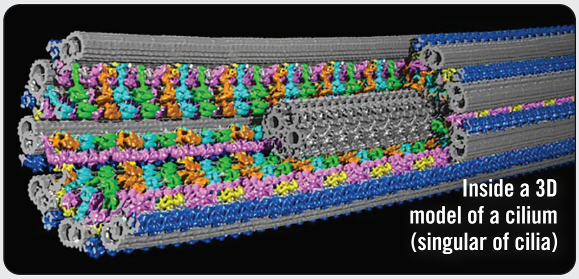


Cool image fact This is a molecular model of the TRPA1 protein, which is involved in sensing pain. It is responsible for the burn you feel on your tongue when you eat hot mustard or wasabi. It's informally known as the "wasabi receptor"!

How scientists created this image Scientists flash-froze the protein by plunging it into liquid ethane to preserve it. A **cryo-electron microscope (cryo-EM)** recorded how the protein deflected electron beams to map the protein's structure. (Cryo- means extreme cold.)

How do cells take out the trash?

Cool image fact Did you notice those stringy things on the cover? Called cilia, they wiggle in a wavelike motion to sweep out debris or propel cells forward. Defects in cilia can cause several diseases, so uncovering how healthy cilia move is an important foundation for developing treatments.



How scientists created this image **Cryo–electron tomography (cryo-ET)** is similar to cryo-EM but used for cell structures that are too big for standard cryo-EM. Scientists capture high-resolution images of the sample tilted at many angles, then combine the images into a 3D model.

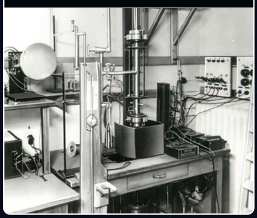
SCOPE IT OUT

Explore technological advancements in scientific imaging through the decades.

With this technique, future scientists were able to map this inner ear protein (a mutation here causes deafness).

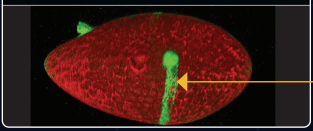
1912 — **X-ray crystallography** is invented.

1937 — The **scanning electron microscope** is invented.



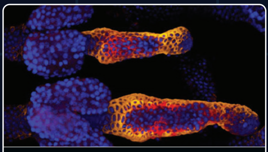
1950s — **Modeling Milestone:** Rosalind Franklin uses X ray crystallography to produce images from DNA fibers, which leads to the discovery of DNA's double helix structure.

1960s — Osamu Shimomura discovers glowing **green fluorescent protein** (GFP) in jellyfish. It's used to label biological parts and track processes under a microscope.



A cell (green) leaves a trail of fluorescent material. Scientists can trace its path and how long its journey took.

Hair follicle stem cells (in red and orange) activating to regrow hair



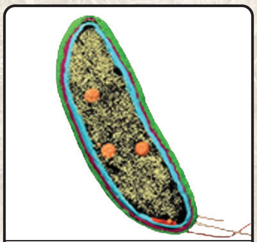
1970s — The first practical **confocal laser scanning microscope** creates detailed images with a focused laser beam.

1980s — **Cryo-EM** is invented, allowing specimens to be examined in high resolution in their natural state without the need for crystallization.

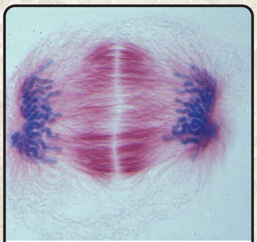
2020 — **Modeling Milestone:** Using cryo EM and improved cameras, researchers break resolution barriers to produce the first image of the individual atoms in a protein.

Caption Challenge

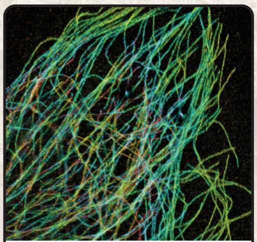
Complete the captions for these microscopic images using concepts you've picked up in class.



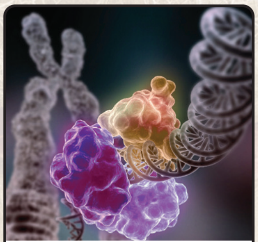
Model of a bacterial __________ created using cryo-electron tomography.



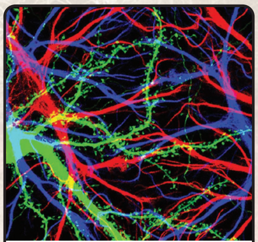
A time-lapse sequence of mitosis in a flower cell. Also known as __________, this process was captured with a light microscope.



These thin, fibrous tubulin proteins help to make up a cell's skeleton, also known as a __________.



Scientific illustration shows an enzyme wrapping around a broken strand of __________ to repair it.



The dendrites of this __________ located in the brain's hippocampus transfer electrochemical signals to the body's central nervous system.

Word Bank Cytoskeleton ◆ Cell Division ◆ Neuron ◆ DNA ◆ Cell

Scientists in the Spotlight

Meet four scientists who use cool imaging tools and tech in their work.

Sudha Chakrapani, Ph.D.

Professor, Case Western Reserve University

Type of Scientist: **Structural biologist**, researching how the brain communicates with the body

How could your work lead to new medicines? We recently solved the first **cryo-EM** structures for a type of serotonin receptor [serotonin is a kind of neurotransmitter that sends messages in the brain]. We went on to show how blocking this serotonin channel could help treat nausea and vomiting in cancer patients.

Christopher Barnes, Ph.D.

Postdoctoral Fellow, California Institute of Technology

Type of Scientist: **Structural biologist**, researching how viral proteins infect human cells

What's the coolest part of your day as a scientist? No question—it's the chance to use high-powered tech to collect datasets! A few years ago, I worked with an **X-ray free electron laser**. At the time, there were only two of them in existence. Sitting at the controls, knowing I was one of only two scientists in the world doing this work—it's so cool!

Shraddha Nayak, Ph.D.

Postdoctoral Fellow, University of Utah

Type of Scientist: **Molecular animator**, using graphic design software, coding, and images of protein structures

Tell us about the tools you use in your work: The **3D animation software** I use has mind-blowing capabilities! It lets me create a setting within a cell, simulate a process that is taking place, and show movements and changes over time. The tools I work with allow scientists to see their hypotheses and communicate their findings.

Melody Campbell, Ph.D.

Assistant Professor, The Fred Hutchinson Cancer Research Center

Type of Scientist: **Biophysicist**, using cryo-EM, physics, chemistry, and math to research how cells communicate

Why do you study proteins? Protein structures not only tell us about shape, but also if the protein is more likely to interact with things like water or things like soap or oil. We can then make small changes to a drug so it binds more tightly in a patient and becomes more effective.

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