

# THE MAJESTIC MICROSCOPIC WORL

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

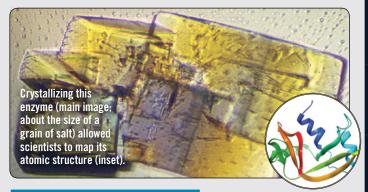
magine you're trying to take a photo of something small—say, a bug with a cool pattern on its back. You zoom in, but the image gets grainy and blurry.

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.

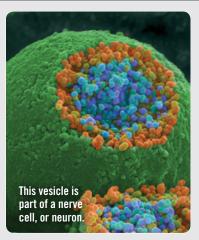
#### How do you digest food?

**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.



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?



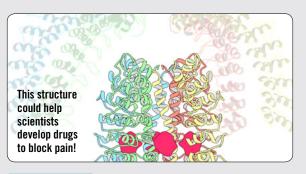
**Cool image fact** This nerve ending has been broken open to reveal vesicles containing chemicals called neurotransmitters that pass messages in the nervous system. Researchers colorized the vesicles in orange and blue to help viewers see the different parts of the image.

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.



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?

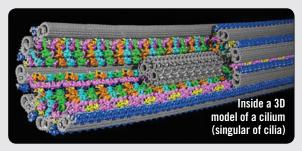


Cool image fact This is a molecular model of the TRPA1 protein, which is involved in sensing pain. It is responsible for the burn you feel on your tongue when you eat hot mustard or wasabi. It's informally known as the "wasabi receptor"!

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. (Crvo- 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.

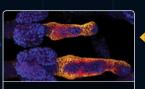
With this technique, future scientists were able to map this inner ear protein (a mutation here causes deafness).



X-ray crystallography is invented.

#### **Modeling Milestone:**

Rosalind Franklin uses X-ray crystallography to produce images from DNA fibers, which leads to the discovery of DNA's doublehelix structure.



The first practical confocal laser scanning microscope creates detailed images with a focused laser beam.

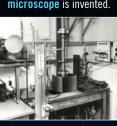
Hair follicle stem cells (in red and orange) activating to regrow hair

#### **Modeling Milestone:**

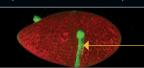
Using cryo-EM and improved cameras, researchers break resolution barriers to produce the first image of the individual atoms in a protein.

1960s 1912 1937 1950s 1970s 1980s 2020

The scanning electron microscope is invented.



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

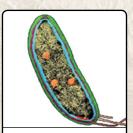


**Cryo-EM** is invented, allowing specimens to be examined in high-resolution in their natural state-without the need for crystallization.

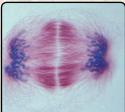
A cell (green) leaves a trail of fluorescent material. Scientists can trace its path and how long its journey took.

# **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.



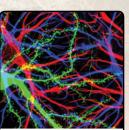
A time-lapse sequence
of mitosis in a flower
cell. Also known as
\_\_\_\_\_\_\_, this
process was captured
with a light microscope.



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

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

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!

how viral proteins infect human cells



# Shraddha Nayak, Ph.D. Postdoctoral Fellow, University of Utah Type of Scientist Melapular enimeter w

**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.



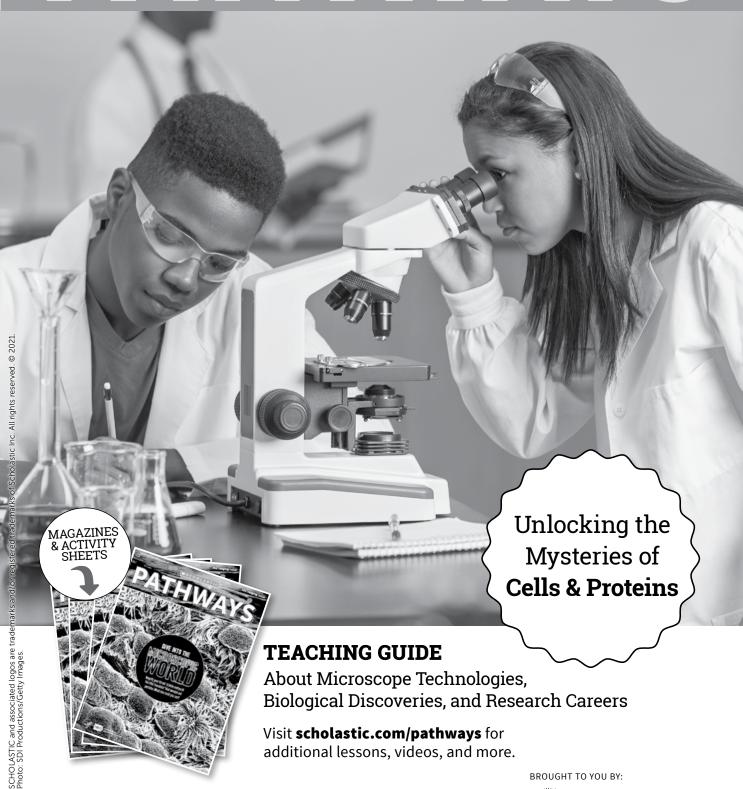
#### Melody Campbell, Ph.D.

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.

# 



BROUGHT TO YOU BY:



## A Closer Look at Scientific Imaging

Discover the stunning images created with advancing microscope technologies. Then have your class create a gallery of colorful scientific illustrations of their own.



#### **Objective**

Students will model cell parts and functions, plus learn about technologies used to capture cellular and molecular structures.

#### **NGSS Standards**

#### Grades 6-8

**MS-LS1-2.** Model a cell's parts and its function.

#### Grades 9-12

**HS-LS1-4.** Model the process of mitosis.

**HS-PS4-5.** Communicate how technological devices use waves to transmit and capture information.

#### **Time**

60 minutes

Allow extra work periods to complete scientific illustrations and imaging research projects.

#### **Materials**

- ► Pin (or image of a pin)
- ► *Pathways* student magazine
- ► Create a Scientific Illustration activity sheet
- ► Research Imaging Tech activity sheet
- ► Imaging Resource sheet (bit.ly/imagingresource)

#### PART A

- **1** Hold up a pin. Ask students how many cells they think could fit on its head. Reveal that about 10,000 cells can fit on the head of a pin.
- **2 Ask:** What kinds of challenges might researchers and structural biologists encounter when studying cells, proteins, molecular structures, or their atoms? Prompt for ideas like: size (too small to be seen without the help of imaging technology), appearance (can be translucent or require staining to visualize), and movement (a biological process could be moving too fast to capture, or the requirements of the imaging technology could kill the specimen, stopping the biological process).
- **3 Distribute** and have students explore the themes in *Pathways* student magazine.
- **4 Have** students read the main text on pages 2–3. After they read, ask them to quickly sketch one of the imaging processes they read about. In small groups or as a class, have them discuss their sketches and collaborate to deepen their understanding of the processes.
- **Direct** students to complete the caption activity on the last page of the magazine. Have them consider advancements like 3D imaging and time-lapse imaging and make connections to ongoing lessons. For example, how might these techniques

#### Inside an Imaging Lab

Meet STEM pros who work with exciting imaging technology:

scholastic.com/pathways/techlab

compare with static 2D images in helping students better visualize energy production in mitochondria or the process of mitosis?

- **Discuss** the career profiles on the bottom half of the last page. Have students imagine they are a structural biologist or molecular animator with access to high-powered microscopes. Ask: What would you want to study?
- **7 Distribute** and have students complete the Create a Scientific Illustration activity sheet, referring to the Imaging Resource sheet if needed. (You may wish to assign Challenge A for middle schoolers and Challenge B for high schoolers.)
- **Hang** or compile completed student diagrams for a physical or digital gallery walk. Have students take in and respond to one another's work.
- **9 Extend** the learning for high school students. Distribute the Research Imaging Tech activity sheet. Once research projects are complete, have students present or share their work in small groups.
- ANSWER KEY Caption Challenge in the student magazine: cell; cell division; cytoskeleton; DNA; neuron



## **◆** Protein Alphabet

Researchers have found a protein in the shape of every letter of the alphabet! Have high schoolers play with the protein alphabet at: **bit.ly/proteinABC** or, for middle schoolers, project and play with the alphabet together as a class!

Name \_\_\_\_\_

### **Create a Scientific Illustration**

Staining is a technique biologists can use to better visualize cells, their components, and their functions under a microscope. Researchers can "label" parts of biological specimens with different dyes to add *color* (in microscopes that use light) or *contrast* (in microscopes that use electrons). A few examples of staining:



- > Crystal violet can be used to tint cell walls purple.
- > Nile blue can stain a cell's nucleus blue.
- > Green fluorescent protein (GFP) can be used to label organelles and proteins a glowing green.

In addition, when scientists combine photos to create a 3D model of a specimen, they may add color to the illustration (known as colorizing) to help viewers differentiate the parts.

#### **Colorizing Cells**

Give the colorizing concept a try for yourself. On a separate piece of paper, complete challenge A or B. **Optional:** Access the Imaging Resource at **bit.ly/imagingresource** to check out brightly colored examples of staining and colorizing.

#### CHALLENGE A CHALLENGE B

Create an eye-catching visual aid that helps its viewers understand the function of a cell and the ways parts of cells contribute to its function.

- ⇒ **Draw** a diagram of a bacterium or a plant or animal cell.
- "Stain" each component of the cell structure a different color.
- Create a key to link your chosen stain color with each cell component.
- ⇒ Provide a brief explanation of the function of each cell component.

Create an eye-catching visual aid that helps its viewers better understand the process of mitosis (cell division).

- Diagram the stages of mitosis.
- "Stain" centrioles, chromosomes, centromeres, the nuclear membrane, and the cell membrane different colors.
- Create a key to link your chosen stain color with each cell component.
- Provide a brief, written explanation for each stage of the process.

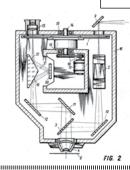
#### **Think About It**

1. What are the advantages of adding color to an image of a microscopic specimen?	

2. What are the limitations of looking at single, static photographs of cells to understanding biological processes?

# **Research Imaging Tech**

Learn more about the imaging technologies researchers use to make basic science and structural biology breakthroughs. Plus, explore some of the educational and career pathways that have led researchers to their areas of study.



Drawing of the first commercialized confocal microscope: the tandem scanning microscope, developed by Mojmír Petráň

# $\left. \int \int \mathsf{SELECT} \ \mathsf{the} \ \mathsf{imaging} \ \mathsf{technology} \ \mathsf{of} \ \mathsf{your} \ \mathsf{choice} \ \mathsf{or} \ \mathsf{one} \ \mathsf{from} \ \mathsf{the} \ \mathsf{list} \ \mathsf{below}. \right.$

- ☐ Confocal Laser Scanning Microscope
- Scanning Electron Microscope
- Scanning Tunneling Microscope
- Cryo-Electron Microscope
- ☐ Lattice Sheet Microscope
- ☐ Fluorescence Microscope

- ☐ X-Ray Crystallography
- ☐ Raman Spectroscopy
- Nuclear Magnetic Resonance (NMR) Spectroscopy
- ☐ Cryo-Electron Tomography
- ☐ Digital Scientific Illustration or Animation (3D or 4D Modeling)

# 2 CONDUCT research to find out:

- How the technology works
- ⇒ Which fields of study it's used in
- ⇒ The imaging result it produces (example: 3D model, molecular-level resolution, etc.)
- ⇒ Examples of specific images it has produced
- A Major milestones or discoveries associated with the technology or its advancement
- ⇒ How it can be used to learn more about life or human health
- Types of careers that use this imaging technology

## PACKAGE and PRESENT your research findings using the method of your choice:



Create a handy
user manual or guide,
with images.



Write a **blog post** or design an informative **webpage**.



**Storyboard** or create a **short video** for presentation to your class.



Write a **journal entry** or **letter** to yourself or a friend.



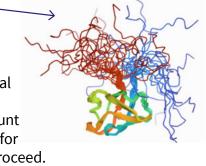
#### **VOCABULARY LIST**

BIOLOGY IMAGING

**DNA** (noun): the molecule found in cells that carries instructions for cell structure and processes in the body. DNA contains genes that are passed on from parents to offspring and give living things their inherited characteristics. The letters *DNA* stand for **d**eoxyribo**n**ucleic **a**cid.

enzyme (noun):

a type of protein
found in animals
and plants that
speeds up chemical
reactions by
reducing the amount
of energy needed for
the reactions to proceed.



**gene** (noun): a small section of DNA that contains instructions, usually for making a specific protein.

**mitochondrion** (noun; plural is mitochondria): an organelle (part of a cell) that converts food and oxygen into energy to fuel the cell.

**neuron** (noun): a cell within the nervous system that transmits information to other nerves, muscles, or gland cells.

proteins (noun): large, complex molecules that are essential for all life processes, playing a key role in the structure, function, and regulation of the body's cells, tissues, and organs.

RNA (noun): the molecule that delivers a copy of the instructions in DNA so that cells can produce proteins according to the instructions. The letters RNA stand for ribonucleic acid.

**crystallize** (*verb*): to cause a material to organize into a crystal form in which its atoms or molecules are arranged in a highly ordered structure.

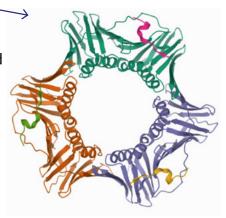
**diffraction** (noun): the slight bending of light, or other waves (like X-rays), when passing around something in its path.

**electron** (*noun*): a particle that orbits the nucleus of an atom and carries a negative electrical charge.

**fluorescence** (noun): light that a substance (like a protein) first absorbs and then emits (gives off).

imaging (noun): techniques used by scientists that make cellular, molecular, and atomic structures and processes visible.

laser (noun): a very narrow beam of light, or a device that uses the vibrations of atoms or molecules to generate light.



**light microscope** (noun): a type of microscope that uses light rays and curved glass lenses to magnify a specimen; also known as an optical microscope.

# TAKE IT FURTHER

Choose five vocabulary words that you think will be hardest to remember, then write a paragraph with them (nonfiction or fiction).

**specimen** (noun): a sample or example of something that is used for scientific study.

structural biologist (noun): a scientist who studies how biological molecules are built. Using a variety of imaging techniques, structural biologists view molecules in three dimensions to see how they are assembled, how they function, and how they interact.

# The Colorful World of Imaging Technology

Check out some of the ways color and contrast can help scientists better visualize tiny specimens, and how this research can help human health!

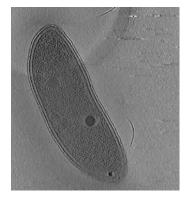
## **Staining and Colorizing Specimens**

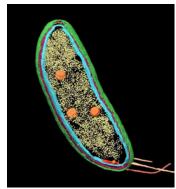
#### **Cryo-ET image before and after colorizing**

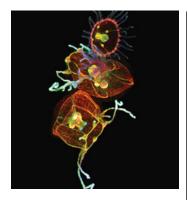
Specimen: Caulobacter bacterium

**Color key:** In the second image, cell membranes are highlighted in red and blue, protein shell in green, ribosomes in yellow, and storage granules in orange.

**Why study this?** By studying this bacterium, scientists learn more about asymmetric cell division—an important factor in our understanding of human disease and the growth of tumors.





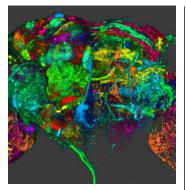


# **Light sheet fluorescence** microscope

Specimen: Jellyfish

**Color key:** Nervous system is stained green. Musculature is stained red. Cell nuclei are stained blue.

Why study this? By studying jellyfish tissues, scientists learn more about the evolution of animals, including humans!



# Confocal microscope + fluorescence

Specimen: Fruit fly brain

**Color key:** To create this digital, 3D color-coded map, scientists labeled the brain's parts with fluorescence, then captured and combined thousands of photos.

Why study this? By studying the brain of fruit flies, researchers aim to learn more about the functions and structures of the human brain.

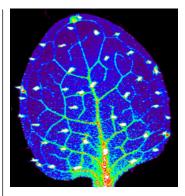


# Scanning electron microscope

Specimen: Leg muscle

**Color key:** Blood vessels are colorized pink (with red blood cells at the bottom). The light brown marks the extracellular matrix (ECM), made up of molecules like proteins that physically support the muscle.

Why study this? Disruption of the ECM is associated with many muscle disorders. Scientists hope to learn more about how the ECM functions and how muscle disorders can be treated.



# X-ray fluorescence technology

Specimen: Leaf

**Color key:** The levels of zinc in the leaf from lowest to highest are marked in blue, green, red, and white.

Why study this? Zinc is required for the function of more than 300 enzymes in the human body. With a goal of improving human health, researchers are investigating how plants distribute zinc to find ways of increasing the zinc content of crops.