HUMAN HEALTH
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THE HUMAN PROTEIN ATLAS: A MOLECULAR JOURNEY INSIDE OUR BODIES TO UNDERSTAND HEALTH AND DISEASE

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YOUNG REVIEWERS:

KAÏKE
AGE: 13

KENZO
AGE: 12

NANA YAW
AGE: 13

In this article, we will talk about a way to explore the intricate universe of the human body—an online resource called the Human Protein Atlas. Using this Atlas as a kind of "map" of the human body, scientists can play the role of modern-day explorers, equipped with advanced tools and techniques. The Human Protein Atlas helps researchers study biological questions involving the various organs, tissues, and cells of the body. The "maps" of the Human Protein Atlas were created using techniques that enable scientists to visualize the locations of specific proteins of choice within organs and tissues. Information contained in the Atlas can help to reveal the mechanisms of health and disease, and here we provide a couple of important examples of problems scientists can investigate using these "maps",

NANAABENA

AGE: 12

NANAYAA

AGE: 10

namely the function of the fallopian tubes and the mysteries of ovarian cancer.

EXPLORING THE BUILDING BLOCKS OF THE BODY

Similar to Vikings or other adventurers exploring undiscovered parts of the world, scientists study the body using special tools, to understand all the parts that make up this amazing structure. They can look at the body's large "building blocks"—organs, like the heart, lungs, and brain that work together to keep us alive and healthy. However, the exploration does not stop there! Scientists can zoom in even further to study deeper levels of building blocks: tissues (Figure 1). Tissues are groups of cells working together to perform the vital functions of organs, like the lung tissues that absorb oxygen when we breathe, or the heart muscle tissue that pumps blood through our bodies.

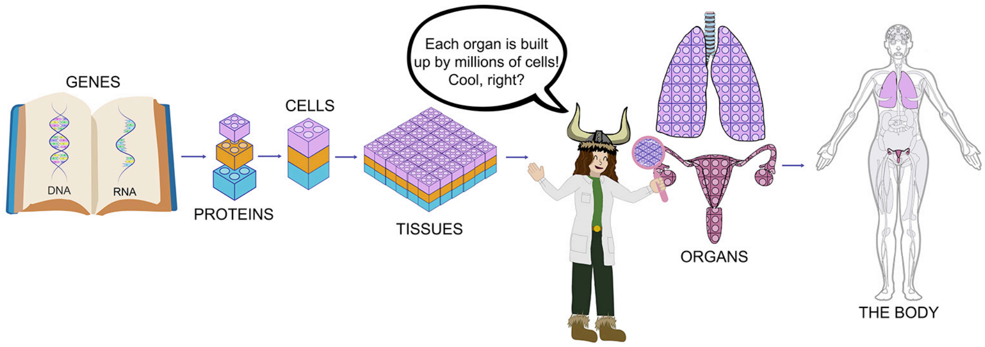

Figure 1

Figure 1

The body consists of building blocks of various sizes. The genes are like an instruction manual, telling the cells how to create the smallest blocks—proteins. When proteins come together, they form the next building block—cells. Cells come in various sizes and shapes, and together form the next block—tissues. Tissues are part of the biggest building blocks—organs. Organs all have unique jobs, such as collecting oxygen from the air (lungs). Together the organs form the body.

Going deeper into the mysteries of the body, scientists can investigate cells, the tiny building blocks of tissues. Each cell contains a special guidebook, in the form of genes. The genes are together an "instruction manual", telling the cells how to behave, what **proteins** to produce, and which functions to perform. The proteins then carry out many different functions depending on where in the body and in which tissue the cell is located (Figure 1).

PROTEINS

Tiny building blocks of life that do many important jobs in our bodies, like helping us grow, stay healthy, and fight sickness.

Scientists in Sweden are building a huge collection of maps of the body called the Human Protein Atlas [1]. This online atlas is free for everyone to use, ensuring that anyone can join the expedition throughout the amazing human body. Like Vikings sailing unknown seas, researchers use the Atlas as a helpful map to find their way. By locating especially interesting proteins, scientists can discover the answers to important medical questions, like finding out what might be causing problems like cancer [2, 3].

The "Tissue" chapter of the Human Protein Atlas explores 44 different types of normal human tissues, helping scientists to understand the body's construction [4]. But how do the Atlas creators generate these maps? They use various technologies to create vivid images, charting the locations of specific proteins within our organs and tissues.

TOOLS TO BUILD THE HUMAN PROTEIN ATLAS

Scientists use several cool tools to explore the tissues and cells of the human body. Data gathered using some of these tools can be assembled into the "maps" of the Human Protein Atlas.

Gathering Tissues for the Tissue Chapter of the Human Protein Atlas

First, scientists gather real human tissues from hospitals. These tissues come from kind people who agree to help science by donating their tissues to research. Sometimes tissues are collected during surgeries performed when a patient needs treatment or to find out what is wrong. Donors' personal details are kept secret to respect their privacy; thus, scientists only know a few things about the donors, like their age. Once scientists have the tissues, they keep them safe in a special wax block called a **formalin-fixed paraffin-embedded (FFPE) block** (Figure 2A). This block helps preserve the tissues for a long time, up to decades, without the proteins breaking down. Scientists can then cut thin slices of the tissue, like cutting a slice of cheese (Figure 2B), put the slices on glass slides (Figure 2C), and look at them under a microscope (Figure 2D).

FORMALIN-FIXED PARAFFIN-EMBEDDED (FFPE) BLOCK

A way to store tissue samples in "wax" and to keep their structure. They can be stored like this for decades.

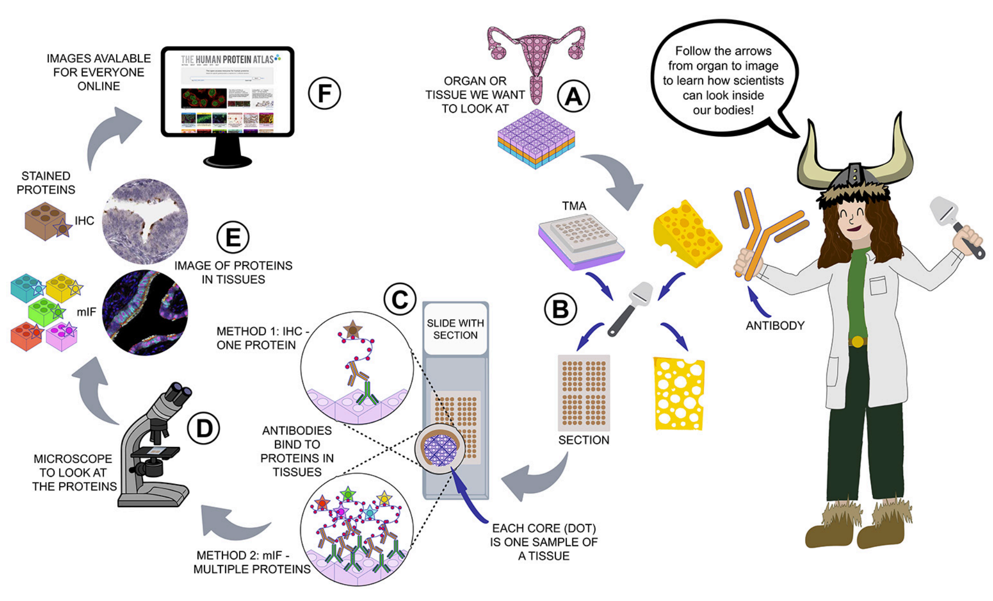

Figure 2

Figure 2

Finding a protein. **(A)** Scientists select a tissue or organ to study. **(B)** They embed the tissue in FFPE, extract tiny cylinders, and place them in a tissue microarray (TMA). Thin slices (sections) are cut like cheese and placed on slides. **(C)** Slides are colored by immunohistochemistry (IHC) for one protein (brown), or multiplex immunofluorescence (mIF) for multiple proteins (various colors), using antibodies. **(D)** Special microscopes capture detailed images, revealing protein locations. **(E, F)** With these pictures, scientists can find where the proteins are in tissues. Images are added to the Human Protein Atlas, providing a resource for other scientists.

Now that the tissues have been collected, let us explore how they can be used to create detailed maps of the human body and its organs.

TISSUE MICROARRAYS

A wax block containing many different samples. This allows for scientists to study many different samples and/or tissues at the same time.

IMMUNOHISTO-CHEMISTRY

A technique scientists use to stain or color proteins using antibodies, allowing them to see the proteins under a special microscope.

ANTIBODIES

Molecules that stick to specific proteins in tissues, helping scientists to find and study those proteins. Antibodies are a normal part of the immune system that scientists have learned how to use in their experiments.

MULTIPLEX IMMUNOFLUORE-SCENCE

This technique makes it possible to see many different proteins at the same time which allows scientists to get an even deeper understanding of the structure of cells and tissues.

Examining Tissues Using Tissue Microarrays

Instead of studying one tissue at a time, scientists can use a technique called **tissue microarrays** (TMA) to examine many tissue samples at once [5]. Imagine having many FFPE blocks, each one containing a preserved tissue sample from a different donor. To study many tissues efficiently, scientists punch tiny cores, like small cylinders, from these blocks—similar to how garlic comes out of each small hole in a garlic press. Each core represents a specific tissue or organ. Then, scientists place these cores into an empty wax block, arranging them in an organized grid pattern (Figure 2B). This block, now consisting of multiple tissue samples, is the TMA. Once the block is prepared, scientists can cut thin sections (like slices of cheese), and place them on glass slides for analysis under a microscope (Figure 2D). This approach lets scientists analyze many tissue samples at once, making their exploration more efficient and helping to save precious patient samples for other research projects.

Finding the Location of Proteins With Immunohistochemistry

Next, to see where specific proteins are located in tissue samples, scientists can use a technique called **immunohistochemistry** (IHC) [5]. IHC uses molecules called **antibodies**, which act like guided arrows, precisely designed to target and stick to the particular proteins the scientists want to find. All antibodies do not match all proteins—they are designed to each find a specific part of a specific protein, allowing scientists to pick and choose which protein they want to see under the microscope by using an antibody that fits that specific protein. When the antibodies find their protein targets, they stick strongly and leave behind a brown-colored stain (Figure 2C). This staining is crucial because it helps scientists to visualize where the proteins are found in the tissues [2], thus creating detailed maps showing where specific proteins are located in various organs. Moreover, IHC enables scientists to determine whether a protein is specific to a particular organ, tissue, or cell type, or if that protein is present in multiple locations and tissues.

Multiplex Immunofluorescence to see Multiple Proteins at Once

In the quest for a deeper understanding, scientists use methods that go beyond conventional IHC, allowing them to study multiple proteins simultaneously, generating an even more detailed map [3]. With one such technique, called **multiplex immunofluorescence** (mIF), scientists target several proteins at the same time using multiple antibodies, each with a different fluorescent color (Figure 2C). The fluorescent colors "light up" multiple proteins at the same time within cells and tissues, providing a richer understanding of their locations and functions (Figure 2E). By studying the complex interactions between proteins, scientists can understand how our cells and tissues function and what happens when things do not work properly. For example, cancerous tumors can express different proteins than healthy cells, making it possible for scientists to visualize cancer cells by targeting those specific proteins.

These techniques, all part of the scientist's toolkit, helped to create the Human Protein Atlas—a guide to understand the body's architecture, open for everyone to use (Figure 2F).

EXPLORING THE HUMAN BODY: A SCIENTIFIC VIKING VOYAGE!

Let us set sail on an exciting journey, where scientists use their tools to explore the human body. These examples are studies made with the antibodies and techniques used to create the Human Protein Atlas.

Voyage 1: Cilia in the Fallopian Tube

The fallopian tubes connect the ovaries to the uterus in the female reproductive system. If you zoom in on the inside of the fallopian tube, there are special cells with tiny hair-like structures called cilia. Cilia help to move eggs from the ovaries to the uterus by pushing them forward. If a fertilized egg reaches the uterus, it can grow into a baby. Scientists use a viewing tool, like mIF, to study the proteins of the fallopian tube cells to understand how they collaborate to take care of the eggs. Each protein within the ciliated cells has its own color in this technique, allowing scientists to map the various parts of the cells to understand how they work together and thereby understanding the structure of the cells (Figure 3A).

Voyage 2: The Battle Against Ovarian Cancer

The ovaries are another part of the female reproductive system, located at the end of the fallopian tubes. Ovarian cancer is a serious form of cancer in which the cells in the ovary start to divide in an uncontrolled way. The symptoms are vague, making this cancer type hard to detect. Using tools like mIF, scientists can see cancer cells spreading like invaders (Figure 3B), but they can also spot cells of the **immune system** fighting back to protect the body from the cancer cells!

IMMUNE SYSTEM

The body's defense team, protecting us against bad germs and sickness.

THE HUMAN PROTEIN ATLAS—A WAY TO GO DEEPER

In conclusion, exploring the body's construction at the microscopic level unveils its fascinating architecture. Scientists, acting as explorers, can use the Human Protein Atlas as a guide to decode health and disease mysteries, increasing the understanding of how cells and proteins work. Hopefully, the Human Protein Atlas will continue contributing to significant discoveries and paving the way for a healthier future.

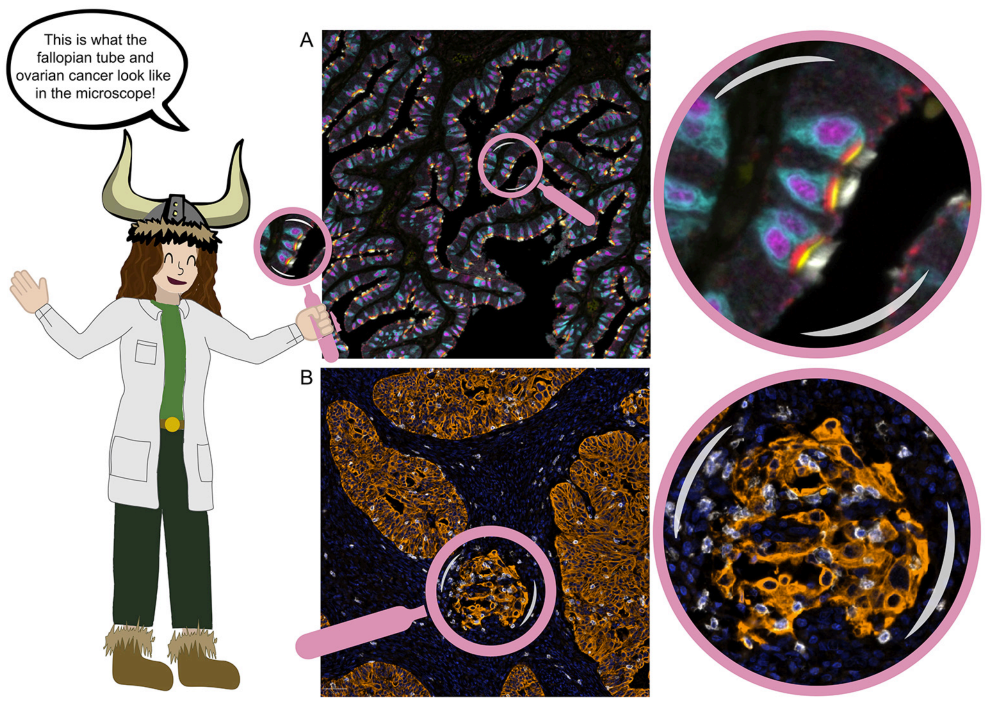

Figure 3

Mapping tissues and cells. **(A)** The fallopian tube. Left: a part of the fallopian tube where five different proteins are stained within the ciliated cells. Right: a closer look at the ciliated cells. The white, yellow, and red color shows the cilia and their different parts, which are small hair-like structures. **(B)** Ovarian cancer. Left: a part of an ovary with cancer cells in orange, immune cells in white, and other cells in blue. Left: a closer look at the cancer cells in orange, which are being fought by the immune cells in white.

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YOUNG REVIEWERS

KAÏKE, AGE: 13

My name is Kaïke. I love football, gaming and eating. I am from Brazil, France, Egypt and have roots in Italy and Syria as well. I have many friends and I love seeing them. I also love anime. My favorite Animés are Naruto, Dragon ball Z and Demon slayer. I am a very good baker and I cook lot of cakes and cookies. My favorite football player is Cristiano Ronaldo and my favorite team is Manchester United and Real Madrid.

KENZO, AGE: 12

Hi I am Kenzo, I am twelve years old, always excited and super friendly. I have a lot of friends and make new friends easily. I like listening to songs and playing video games. I also really like fighting and self-defense. My favorite hobby is parkour. At school, I enjoy sports, arts, math and the breaks. I often express my thoughts and talk while the teacher explains so time goes faster. I love reading comics and reading about space, black and white holes.

NANA YAW, AGE: 13

Nana Yaw is a 13 year old 8th grader and he loves everything football. In his spare time plays video games especially "FC Mobile". Nana Yaw also loves animals especially dogs. He enjoys science and aspires to be a computer scientist.

NANAABENA, AGE: 12

Nanaabena is 12 years and a 7th grader. Her hobbies include dancing and having a good chat with her friends. She loves cooking and aspires to be a food scientists. Nanaabena is very assertive and loves asking questions to satisfy her curiosity.

NANAYAA, AGE: 10
Nanayaa is an intelligent 10-year-old girl and a 5th grader. She loves singing and reading. Her favorite book is Oliver Twist. Nanayaa is much focused which makes her able to complete tasks on time.

AUTHORS

FILIPPA BERTILSSON
I am a Ph.D. student interested in how the human body works, why it works the way it does, and how we can battle diseases. I want to explore this further with my research, which is focused on female reproduction. I come from Sweden, where I grew up on a farm full of cows that I love to pat every time I visit my family. In my free time, I love to be outdoors, whether it is hiking or enjoying a coffee in the sun. Some other interests of mine are reading, painting, cooking, and playing video games.

CECILIA LINDSKOG
I am a research group leader and have always been interested in understanding the human body and what happens when we get ill. My fascination for the microscopic universe led me to the Human Protein Atlas project, and now I am leading an amazing team of scientists that each help with different puzzle pieces of mapping the human body! When I am not looking at microscopic images, I love creating other types of images, either with my camera or by drawing them. My favorite place is the forest, and I become really happy when I can bicycle, even when it is snowing!

LOREN MÉAR
I am a postdoctoral researcher studying ovarian cancer, puberty and menopause to better understand female biology. When I am not at the university, you will catch me dancing to music, making a splash in the pool/lake/sea, getting lost in a good book, baking up treats for friends and family, and hanging out with my purr-fect cat companions—whether in France or Sweden! *loren.mear@igp.uu.se