The map of the body's proteins

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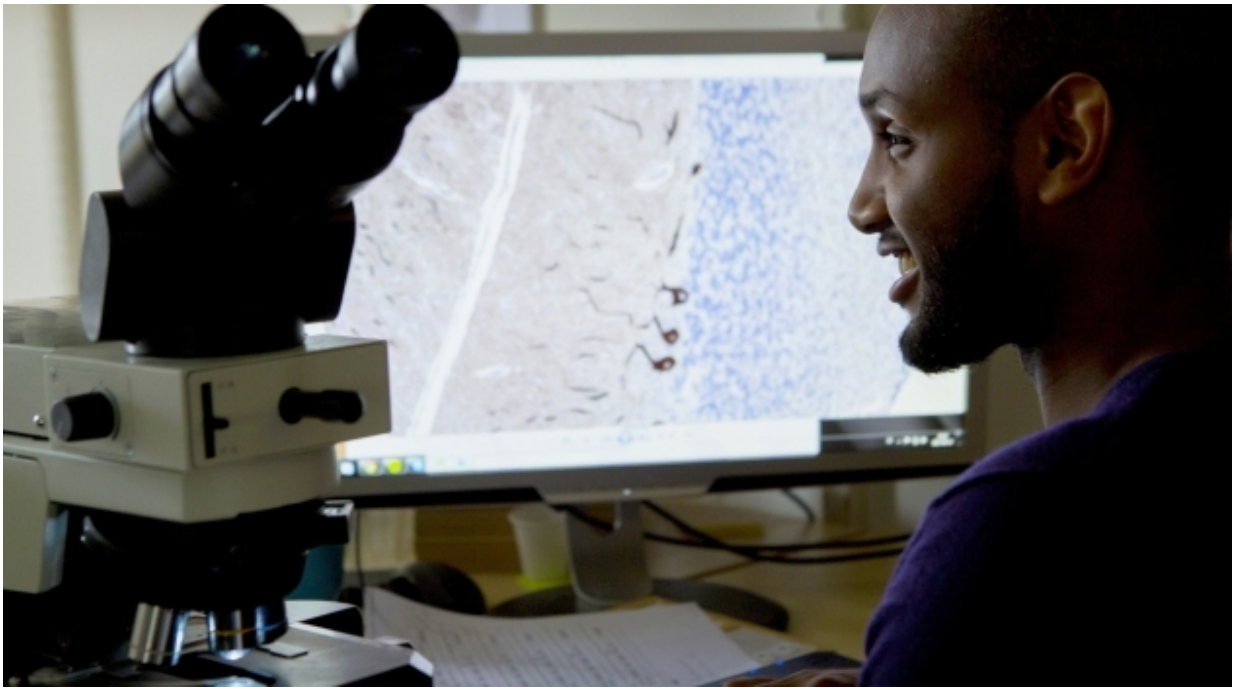

The images are reviewed by researchers and the job is done entirely manually. Here, Groom Alemayehu reviews an image. Credit: Mikael Wallerstedt

Finished after 12 years' work: A pictorial atlas of the body's building blocks; proteins. A total of 13 million images have been collected into a searchable database in a collaboration which has involved institutions including KTH Royal Institute of Technology and Uppsala University.

'This almost complete list of the body's proteins is a major research

resource', said Mathias Uhlén, professor at KTH, during the press conference for the Internet launch of the protein atlas.

The atlas is free to use by everyone who wants to know more about the roughly 20,000 proteins found in the human body.

'Eleven years ago, human genes were mapped. This is a continuation of that project. If you imagine the genes as the design of a house, the proteins are the building blocks that the house consists of', explains Mathias Uhlén.

The mapping process shows that human proteins are expressed in all major tissues and organs—such as the brain, heart, liver and kidneys—and also shows which proteins are expressed in all cells.

To carry out the project, researchers at KTH developed antibodies which can find a particular protein. The next step was to test the antibodies on tissue samples at the Department for Immunology, Genetics and Pathology in Uppsala.

The test results were then scanned in and collected in a searchable database which is open for anyone to use. On the images, the proteins are clearly visible as they have been coloured brown.

It is possible to zoom in and examine the images in detail over the Internet, like having a microscope in your computer. You can search for a protein and see where it occurs, or search by organ.

During the mapping process, it was discovered that a number of proteins are present in all cells; a kind of bodily cleaning process. Around half of our proteins are present in all of the body's cells; these are known as 'basic proteins'. Other proteins most commonly occur in one organ, but the researchers discovered that there are relatively few proteins which

are unique to a certain tissue.

'This is important knowledge for the pharmaceutical industry and may explain some of the problems and side-effects associated with some pharmaceuticals', says Mathias Uhlén.

Professor Fredrik Pontén of the Department for Immunology, Genetics and Pathology in Uppsala has been involved since the start.

'It's really great; it's wonderful to have 'finished', so to speak. We have worked for 12 years and created something which will be of great use to many people. It has been a fantastic example of team work, with researchers from different backgrounds and knowledge contributing to ensure that the project has constantly developed in the right direction.'

Who will use the protein atlas?

'Above all basic researchers, but also clinical researchers, the pharmaceutical industry and biotechnology companies. I hope that it will be used a great deal within medicine, to find both new medicines and diagnostic methods.'

And it seems as though more and more people are discovering the protein atlas. In addition to the 300 scientific articles which have already been published within the project, an average of two articles are published every day by external users.

Even though the protein atlas can be considered as finished, the work continues. Cecilia Lindskog Bergström, site manager in Uppsala, explains:

'We will look in more depth at tissues we didn't examine earlier. Up to now we have looked at 44 different normal organs, but for example

there are other parts of the brain and retina which we didn't investigate and there are still proteins which we haven't found in any of the tissues studied. We will also carry on with the cancer atlas and continue with more detailed research studies.'

Around 30 people are working on the project at Uppsala. The group includes both research engineers, researchers, PhD and post-doctoral students within the fields of biotechnology, biology and medicine. The work is currently under way to complete and publish a large number of articles.

'Our role in the project is above all linked to the medical and clinical aspects. Medical background knowledge is required to interpret what we see in the microscope', says Fredrik Pontén.

'Proximity and access to biobanks have been extremely important, as has the development of techniques for analysing gene expressions on both the RNA and protein level.'

In the lab at the Rudbeck Laboratory, work is taking place at different stations. First, small pieces of tissue must be punched out of paraffin blocks and then a tissue array of 72 small tissue samples must be manufactured. This is thinly sliced and placed on a glass slide.

The samples include both healthy and cancer tissues—from operations carried out at Uppsala University Hospital.

When the slide with the tissue samples is ready, it is sprayed with a solution containing antibodies. These are 'coloured' with antibodies which bind to a particular protein. When the antibody has bound to the protein, it appears brown.

This stage is automated and takes place in a large machine.

'Here we can colour samples with 48 antibodies simultaneously. This means large volumes, so we must have barcodes on each glass slide showing which antibody should be used. We colour hundreds of glass slides every day', explains Cecilia Lindskog Bergström.

The images are then scanned in and an enlarged version can be reviewed on the computer screen. Several researchers are reviewing images. The job is done entirely manually. They look at the screen and decide whether or not the protein is sufficiently visible on the image.

'For each protein, we use data from 144 individuals with normal tissue and 216 individuals with cancer tissue, so it takes several hours to review.

In any case, we've now reached the first milestone. After 12 years' work, we have a clearer picture of human proteins and their role in the body.'

At the press conference, Professor Mathias Uhlén was asked: What will you have achieved ten years from now?

'We now have the proteome, but that's only the start of understanding the magic of the human body', he replied. We will devote many years to this. If you are a researcher, this is a good field to enter for the next 50 years.'

Provided by Uppsala University