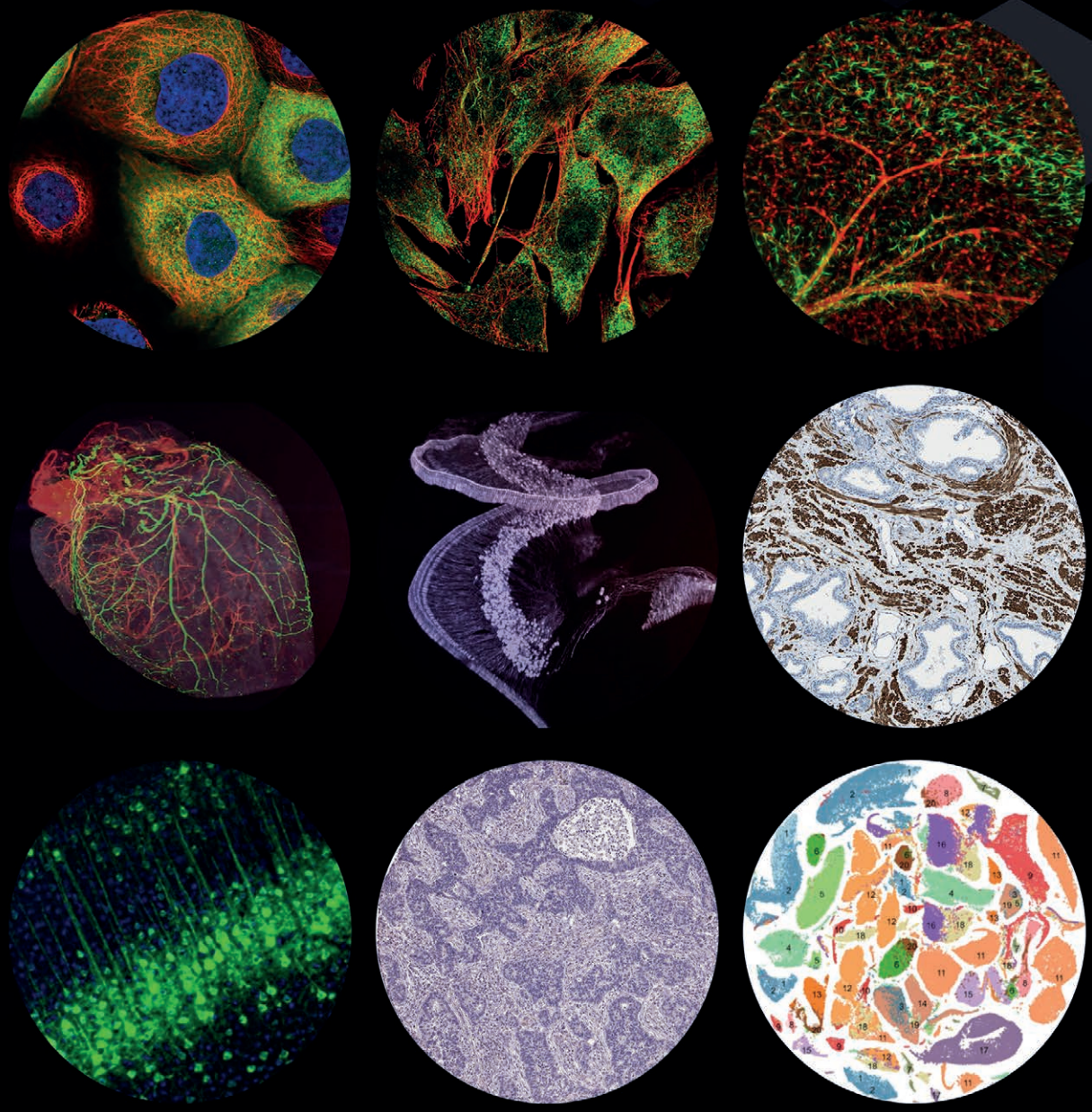


The Human Protein Atlas Program

The first 20 years

HPA consortium

September 2022

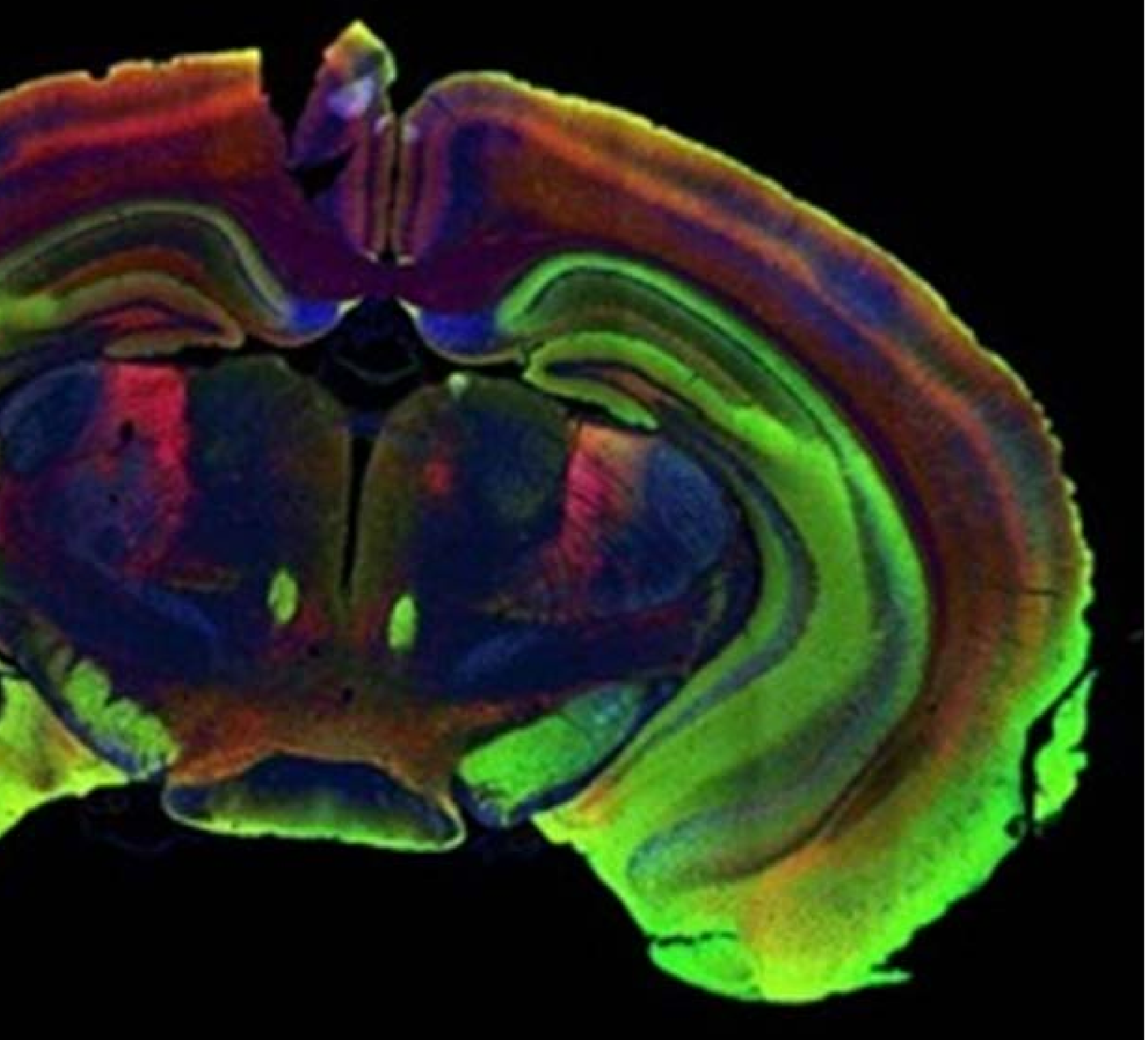


Table of content

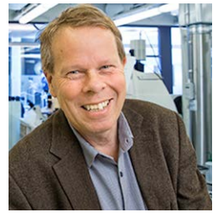
20 years with the Human Protein Atlas

The Human Protein Atlas (HPA) journey started in 2003 with generous support from the Knut and Alice Wallenberg Foundation (KAW). This funding has continued to the present day. The project was expanded to engage research groups at KTH, Uppsala University, Karolinska Institutet, Stockholm University, Chalmers University of Technology, Sahlgrenska Academy, Linköping University, and Lund University, and in addition, several international collaborations were initiated with research groups in Europe, the United States, South Korea, China, and India.

The aim of the program is to map all of the human proteins in cells, tissues, and organs, using integration of various technologies. All the data in this knowledge resource is open-access and free to use for scientists in both academia and industry to explore the human proteome.

The HPA consists of various separate parts, each focusing on a particular aspect of analysis of human proteins. In 2005, the first version of the HPA was launched, and in 2010 the main operation of HPA was moved to the national infrastructure Science for Life Laboratory (Stockholm). In the last decade, several separate parts of the Atlas were launched, five of them accompanied by articles in one of the world´s most prestigious journals, Science. In 2021, a new Single Cell Atlas was published and there is a plan to launch a new Human Disease Blood Atlas in the end of 2022.

The Human Protein Atlas is now one of the most visited biological databases in the world with more than 350,000 visits per month both from industry and academia. The HPA program has already contributed to tens of thousands of publications in the field of human biology and disease and has been selected by the organization ELIXIR (www.elixireurope.org) as a European core resource, due to its fundamental importance for the wider life science community.



Mathias Uhlén, PhD
Director of the Human Protein Atlas program

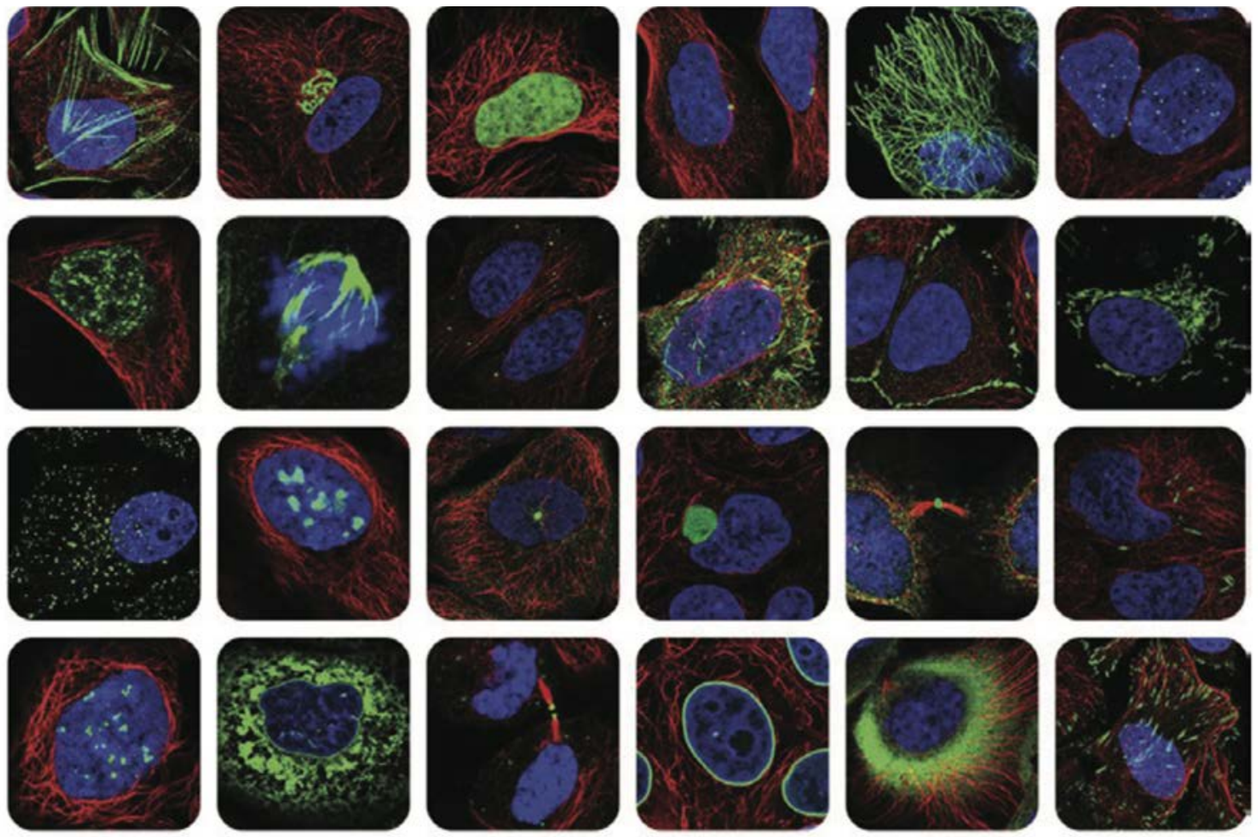
The power of proteins

It was at a White House ceremony 20 years ago, on June 26, 2000, that President Clinton announced the successful sequencing of the human genome. Clinton was joined by Francis Collins, then director of the National Human Genome Research Institute, and Craig Venter, founder and CEO of Celera Genomics. At the time, there were high hopes that building this database of genomic knowledge would rapidly lead to new discoveries and new treatments for diseases. The heavy weight of reality, however, soon set in with the recognition that although we had the blueprint in hand, it didn't tell us much about the biochemical pathways that make cells tick or what, for instance, makes a liver cell so different from a neuron. This puzzle has been likened to having the instructions for manufacturing the millions of parts that make up a Boeing 747, but no guidance on how they all fit together.

Although the DNA code tells us what proteins a particular cell might make, it offers only subtle clues about where, when, and how much of that protein the cell should manufacture. Furthermore, it is these proteins, and not the DNA, that carry out cellular functions and serve as the final arbiters and gatekeepers for all biochemical processes.

The excitement of that announcement two decades ago led many to shift their focus toward genomics. Companies were even vying to copyright parts of DNA. Yet others were convinced that proteins ultimately held the key to understanding normal cellular function as well as disease-related dysfunction. Around the same time that the sequencing of the human genome was being announced, a group in Sweden led by Dr. Mathias Uhlén was embarking on the arguably more ambitious task of creating the Human Protein Atlas (HPA), a catalog of every protein in the human body. While it depended on sequence information provided by the Human Genome Project, the HPA program also augmented the genome efforts, shedding light on the apparent paradox that while only about 20,000 protein-encoding genes have been identified, it is clear that many more proteins exist. The atlas offered a free, open-access knowledge resource that gave researchers valuable insight into the expression levels and locations of all human proteins—and it continues to do so today.

Sean Sanders, Ph.D.
Director and Senior Editor, Custom Publishing
Science/AAAS

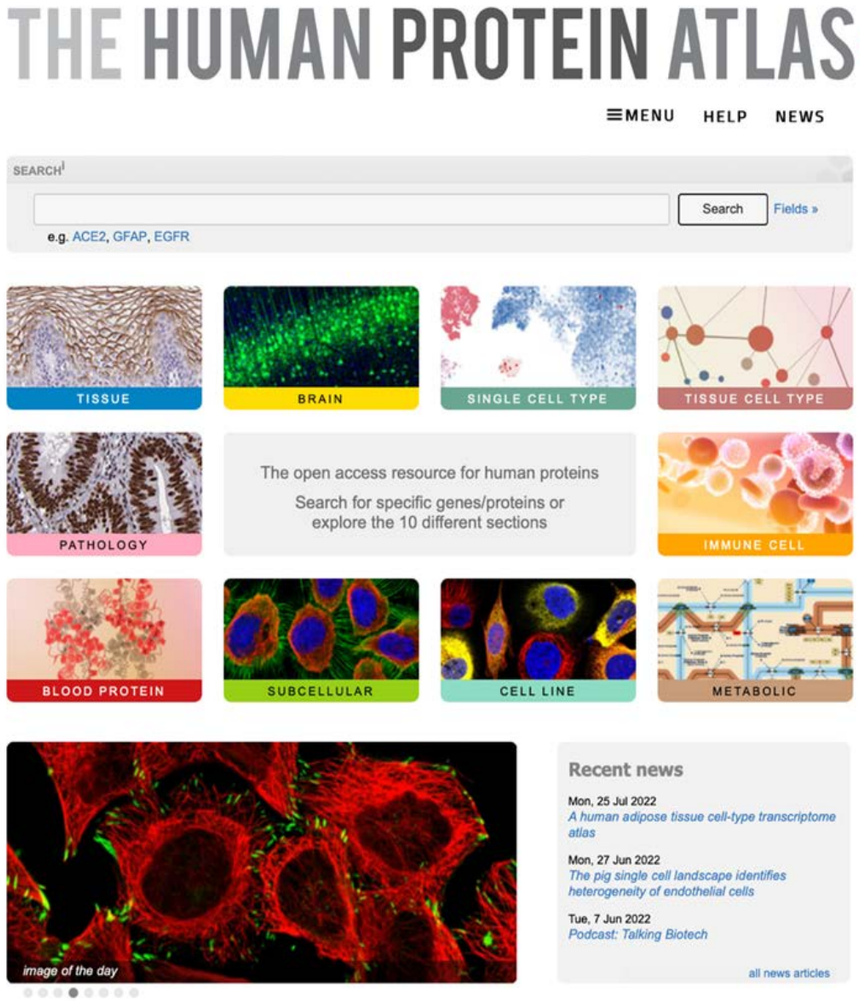


Research program, aims and objectives

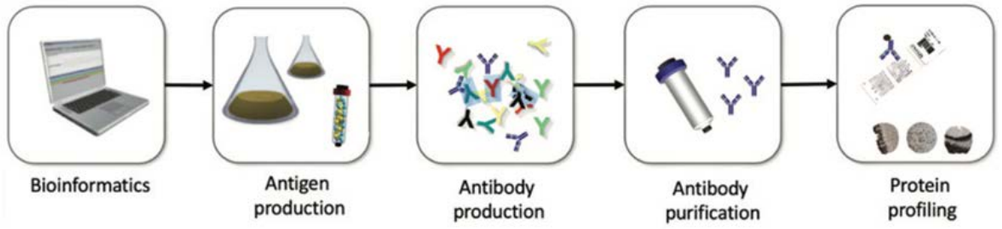
The HPA program started in summer 2003, upon receipt of funding from the Knut and Alice Wallenberg Foundation (KAW). In the proposal (2002), the following questions were asked: "What is it that makes a kidney a kidney? And what makes a heart a heart? All cells, regardless of whether they are in a kidney or the heart, contain the same genetic material and genes. However, different genes are active in the various cells. This leads the cells to have entirely different functions. Some become nerves, others begin to produce insulin. If researchers are to understand how our bodies work, it is these differences they need to investigate, since the proteins account for all activities in the body. They build muscles and tendons, catalyze chemical reactions, send signals all over and much more."

The aim of the Human Protein Atlas program is thus to contribute to the holistic understanding of all the proteins encoded from our DNA. The objective of the Swedish-based program is to map all the human proteins in cells, tissues, and organs using integration of various omics technologies, including antibody-based imaging, mass spectrometry-based proteomics, transcriptomics, and systems biology. The ultimate aim for the project is a complete understanding of the functions and interactions of all proteins and where in the different cells and tissues they reside. So far, we have launched different sections with manual annotation, including millions of web pages and millions of high-resolution microscope images, to allow individual researchers both in industry and academia to explore the proteome space across the human body. In the last decade, the Human Protein Atlas has launched 10 different sections all encompassing different aspects of the human proteins:

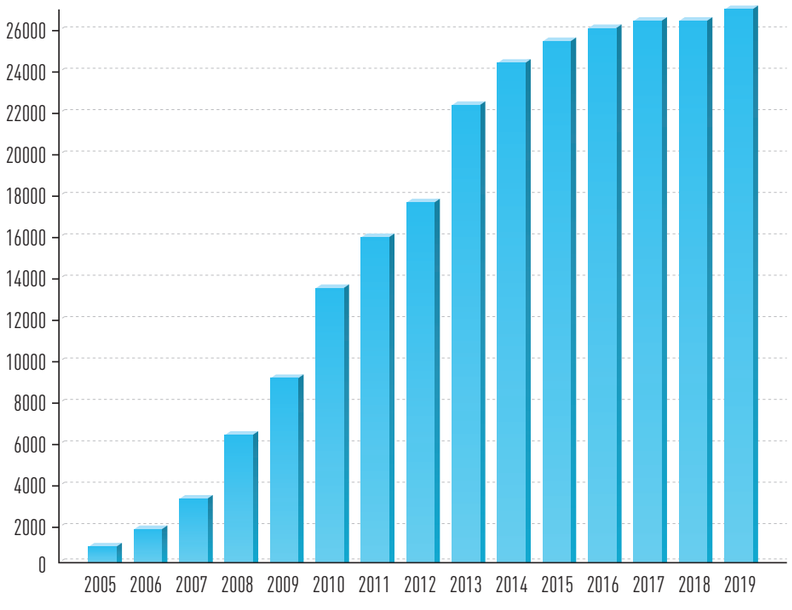
Section	Launched	Description
Tissue	2015	The distribution of the proteins across all major tissues and organs
Subcellular	2017	The subcellular localization of proteins in single cells
Pathology	2017	The impact of protein levels for the survival of patients with cancer
Immune Cells	2019	The expression of protein-coding genes in immune cell types
Blood Protein	2019	The proteins detected in blood and proteins secreted by human tissues
Brain	2020	The distribution of proteins in various regions of the mammalian brain
Metabolic	2020	The expression of protein-coding genes in the context of the human metabolic network
Cell Line	2021	The expression of protein-coding genes in human cell lines
Single Cell Type	2021	The expression of protein-coding genes in single human cell types based on single cell transcriptomics
Tissue Cell Type	2021	The expression of protein-coding genes in human cell types based on bulk RNAseq data



The Human Protein Atlas resource (www.proteinatlas.org)



The unique HPA pipe-line for mapping the human proteins



The number of generated, validated and published antibodies on the Human Protein Atlas

Scientific approach – three major phases

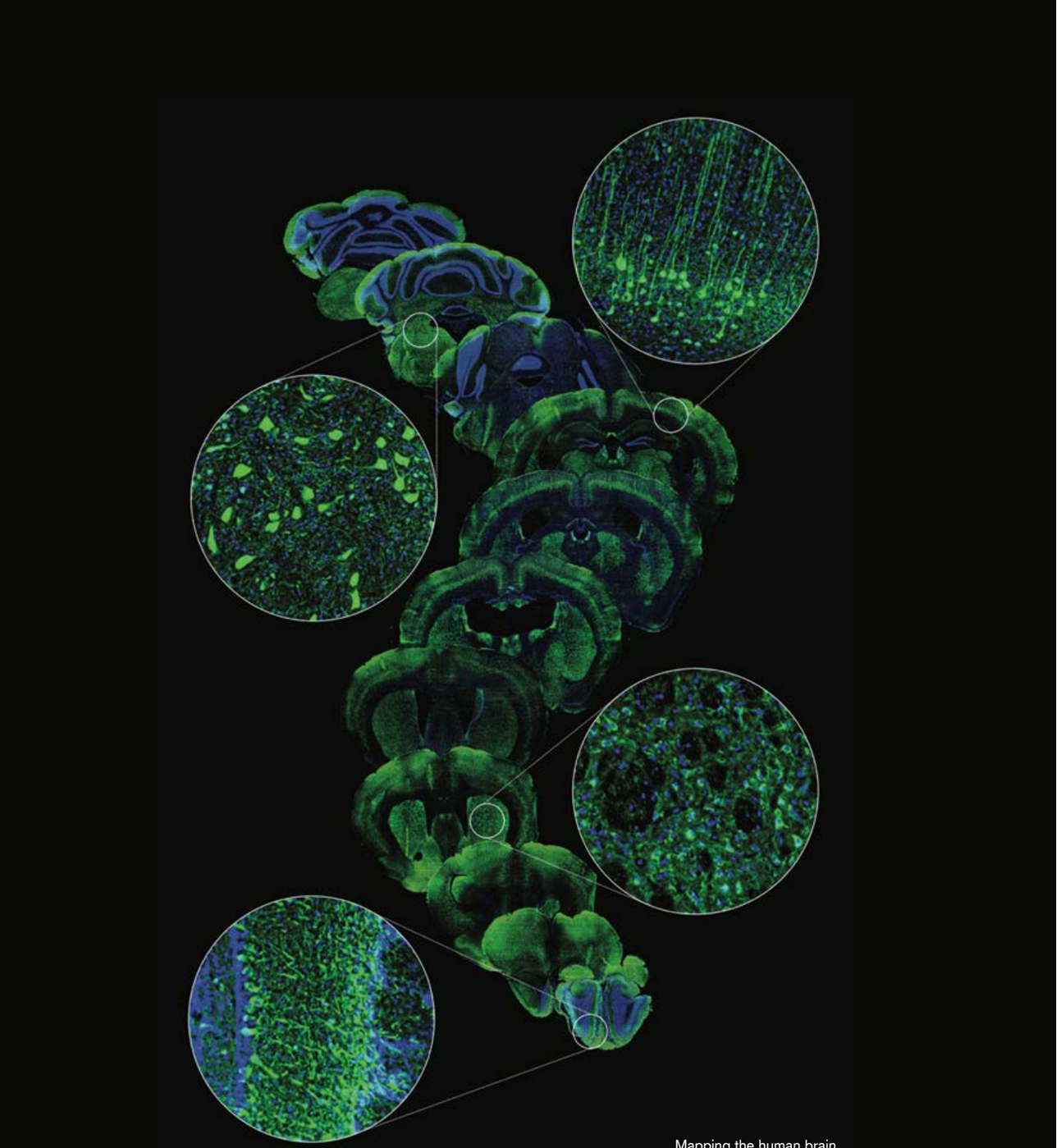
The program can be divided into three separate phases.

First phase (2003-2012) – making antibodies. The focus in the first decade was on generating antibodies to a representative protein from all protein-coding genes defined by the genome project. A unique pipeline was set-up to generate antibodies and protein profiles corresponding to all proteins of humans (see figure). The objective has been that all images should be manually annotated by a certified pathologist.

A web-based annotation tool was developed taking advantage of all tissue images being scanned to generate high resolution digital images. Several "annotation jamborees" was organized in which a large number of Scandinavian pathologists came together and performed annotation of hundreds of thousands of pathology images. However, due to the increased throughput of images, a new strategy to keep up with the production of images was necessary. A dedicated site with pathologists was set-up in Mumbai, India and this site has now annotated more than 10 million images. In the figure (left), the accumulated number of validated and published antibodies used to perform the protein profiling is presented. By the end of the first phase, antibodies representing almost all protein-coding genes had been generated and validated.

Second phase (2013-2022) – integration of omics. The focus in the second decade was on integration of hundreds of millions of data points from different sources and use systems biology to generate various dedicated sections. The data included, apart from original antibody-based images, targeted proteomics using mass spectrometry, transcriptomics using next generation sequencing, analysis of single cells using cell sorting and microdissection of tissue samples, with a focus on the brain. A large number of launches were made during this period, always accompanied by publications in high ranked international journals. The number of visitors to the Human Protein Atlas increased dramatically during this period and the resource became one of the most visited biological databases in the world.

Third phase (2023-) – AI-based life science. The focus in the third phase will be to use data-driven life science to integrate both internal and external data using various AI-based tools to analyze and annotate the human proteome. We plan to continue with annual updates of the open access resource and to collaborate with complementary efforts around the world. The ultimate aim is to create a comprehensive catalogue of the human building-blocks, including function, interactions, structures and localizations in cells, tissues and organs. Our objective is to continue to be one of the most important international resources for information about human proteins both for academia and industry.



Mapping the human brain

The most important scientific milestones

Some of the most important milestones in the HPA program

2003 The HPA first receives funding from the Knut and Alice Wallenberg Foundation. Support has continued to the present day.

2005 The first version of the Human Protein Atlas (www.proteinatlas.org) portal is released. The portal has been updated annually.

2008 The Antibodypedia portal is launched to allow sharing of information on antibody validation. The portal now contains information on more than 4 million antibodies.

2010 A major milestone is reached: inclusion of 50% of human proteins in the atlas.

2015 The Tissue Atlas is launched, providing expression profiles of human tissues and organs. The article (published in Science) is one of the most cited articles from Europe in the last decade (more than 6,000 citations).

2016 The International Working Group for Antibody Validation (IWGAV), chaired by Mathias Uhlen, proposes guidance for reproducible validation of antibodies.

2017 The Subcellular Atlas and the Pathology Atlas are published.

2018 The HPA database of images is used for deep learning, utilizing a citizen-science approach involving 32 million images and input from more than 300,000 gamers.

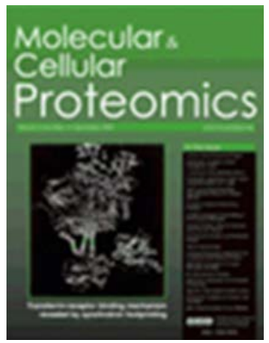
2019 The first annotation of the proteins secreted from human cells (the secretome) is published. The Blood Atlas is published on human immune cells.

2020 The Brain Atlas is published showing expression profiles in the different parts of the mammalian brain by comparing data from humans, pigs, and mice. The Metabolic Atlas is also published with manually curated metabolic pathway maps.

2020-2022 The HPA consortium is engaged to support the fight against the coronavirus pandemic, including the development of diagnostics and therapeutic applications.

2021 The Single Cell Type Atlas is published showing single cell data across various tissues and organs in the human body. The new resource contains a lot of AI-based information, including new ways to functionally annotate the human proteins.

2022 A new resource called the Human Disease Blood Atlas will be launched in the end of the year. The first version will be focused on a pan-cancer effort, that in the near future will be followed by analysis of other diseases, such as cardiovascular, autoimmune, neurodegenerative and infectious diseases.

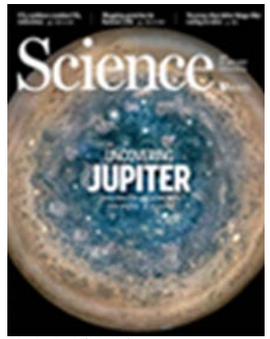


Uhlen et al (2005)

Uhlen et al (2010)

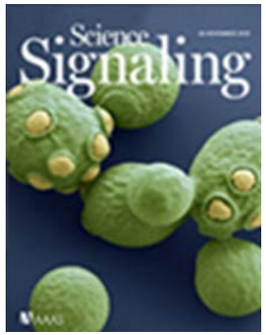
Marx (2014)

Uhlen et al (2015)



Thul et al (2017)

Uhlen et al (2017)



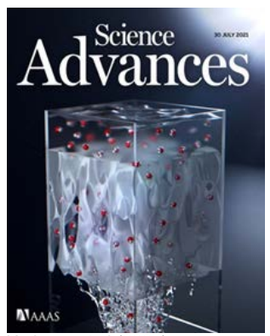
Uhlen et al (2019)

Uhlen et al (2019)

Sjöstedt et al (2020)

Mahdessian et al (2021)

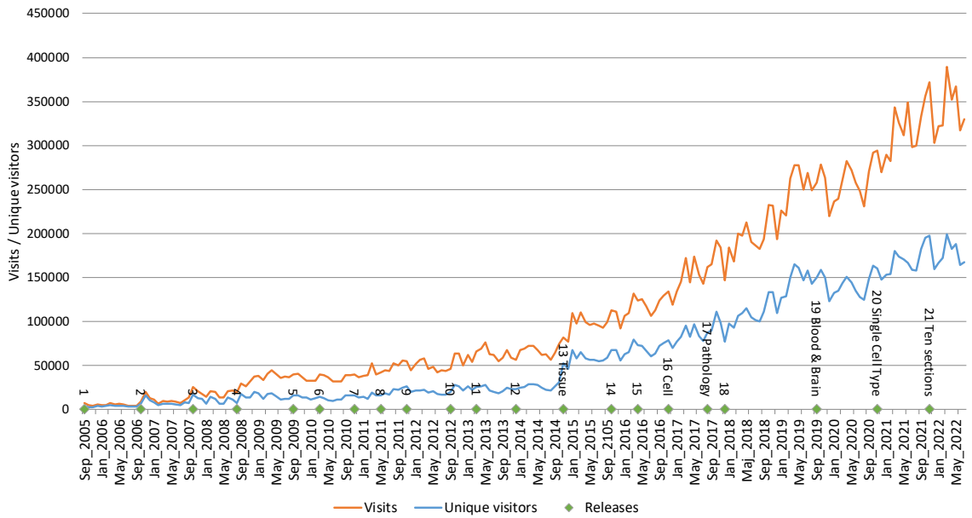
Mahdessian et al (2021)



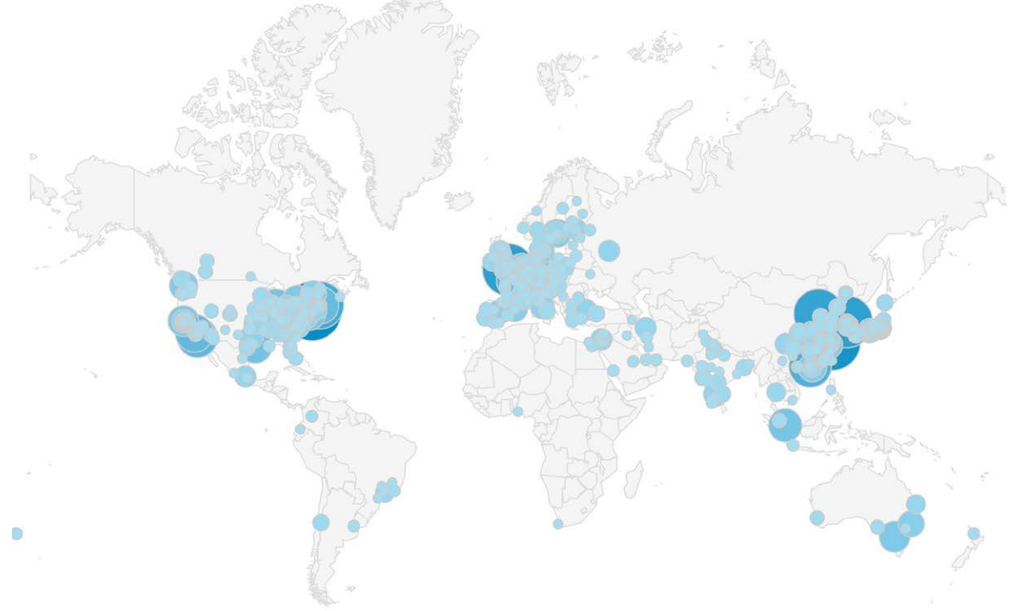
Karlsson et al (2021)

Major launches

Launch	Year	Description	Reference
First Protein Atlas	2005	First launch covering 700 proteins	Uhlen et al, Mol Cell Proteomics
”Ten in ten”	2010	Half (10,000) of the protein-coding genes completed	Uhlen et al, Nature Biotechnology
Tissue Atlas	2015	Protein and RNA profiles in 32 tissues and organs	Uhlen et al, Science
Subcellular Atlas	2017	The subcellular localization of 12,003 proteins in single cells	Thul et al, Science
Pathology Atlas	2017	The impact of protein levels for the survival of patients with cancer	Uhlen et al, Science
Blood Atlas	2019	Protein and RNA profiles in flow sorted immune cells and proteins detected in blood	Uhlen et al, Science
Brain Atlas	2020	The distribution of proteins in various regions of the mammalian brain	Sjöstedt et al, Science
Metabolic Atlas	2020	The expression of protein-coding genes in the context of the human metabolic network	Nielsen et al, Science Signalling
Single Cell Atlas	2021	The expression of protein-coding genes in single human cell types	Karlsson et al, Science Advances
Disease Blood Atlas	2022	The protein profiles in the major human cancers	Unpublished



The number of visits to the HPA resource every month since the start

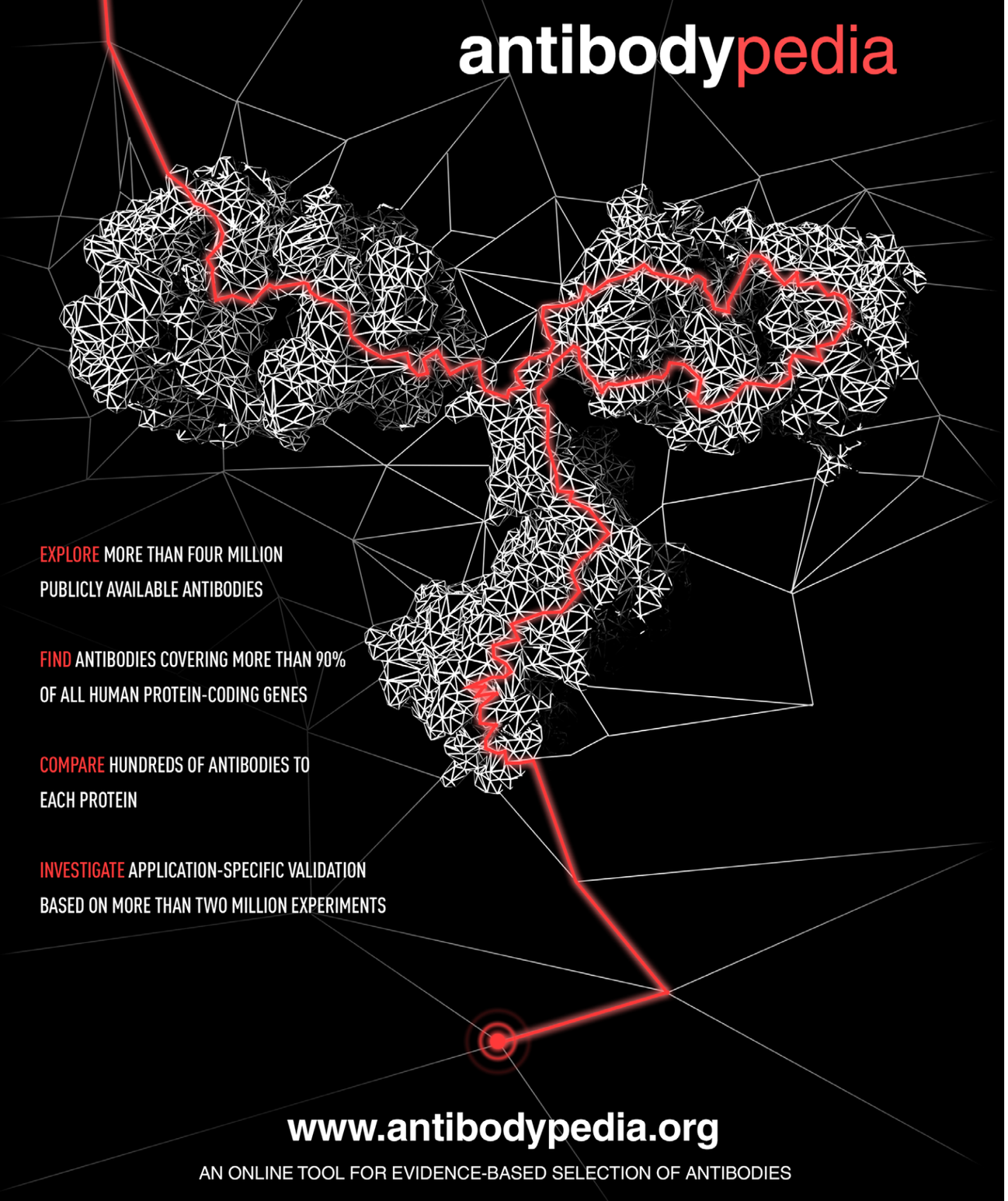


The location (cities) of researchers visiting the HPA resource

One of the largest biological databases in the world

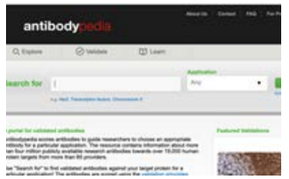
The Human Protein Atlas harbors more than 10 million annotated pathology images and more than 15 million web pages. It is one of the most visited biological databases in the world (see figure) and it has been selected by the EU-infrastructure program Elixir to be a core resource of fundamental importance for the life science community. The resource is used by researchers around the world (see figure).

elixir Core Data Resource



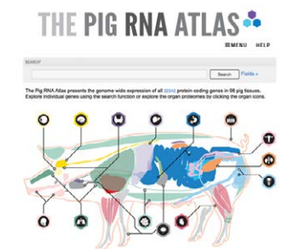
Affiliated Atlases

The Human Protein Atlas consortium has also developed four affiliated resources:



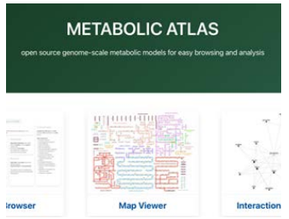
Antibodypedia - A portal for validated antibodies

Antibodypedia scores antibodies to guide researchers to choose an appropriate antibody for a particular application. The resource contains information about more than four million publicly available research antibodies towards over 19,000 human protein targets from more than 85 providers.



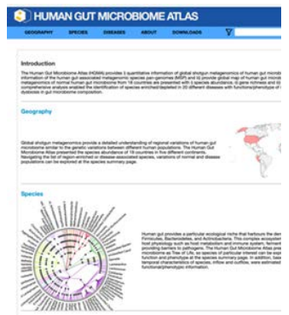
Pig RNA Atlas – The resource for pig research

The atlas presents the genome-wide expression of all 22,343 protein-coding genes in 98 pig tissues. An educational summary page is included, that describes the background of using pig as a model in biomedical research. Different human disease genes are described based on the organ system they are related to. The Pig RNA Atlas is a resource that can be used for studying the body-wide expression similarity and specificity to human in order to evaluate pig as a disease model.



Metabolic Atlas - resource for genome scale metabolic models

Metabolic Atlas is an open access resource providing visualizations and comparisons of the models and links to algorithms, other databases, and more general software applications. The atlas is a collaboration with Chalmers University and it is intended to be used for applications in metabolomics, clinical chemistry, biomarker discovery and general education. In short, the vision is to create a one-stop-shop for everything metabolism related.

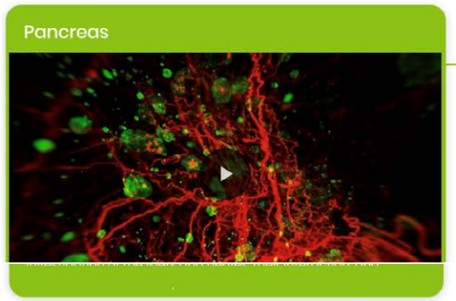


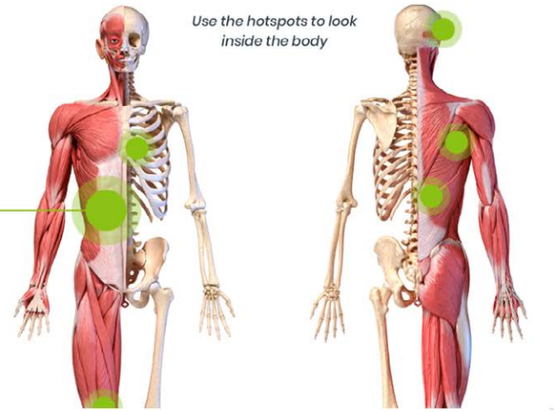
Microbiome Atlas – the microbiome in human health and disease

The Human Gut Microbiome Atlas is a program that aims to analyse the human microbiome data from human oral and gut samples obtained from several disease and healthy cohorts by integration of metagenomics and other omics data using systems biology. All the data in the knowledge resource is open access to allow scientists both in academia and industry to freely access the data for exploration of the human microbiome. In this context, in-depth analysis of the impact of the gut microbiome on health and disease will be used to facilitate studies to reveal the key role of the gut microbiome in human well-being. The resource is a collaboration between HPA (SciLifeLab) and King´s College, London UK.

Journey into the body

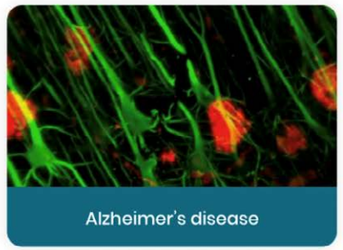
3D movies were generated using resources from the HPA program to visualize different structures in mammalian tissue. Follow the links below to join our journey of discovery.





Journeys into human neurological diseases

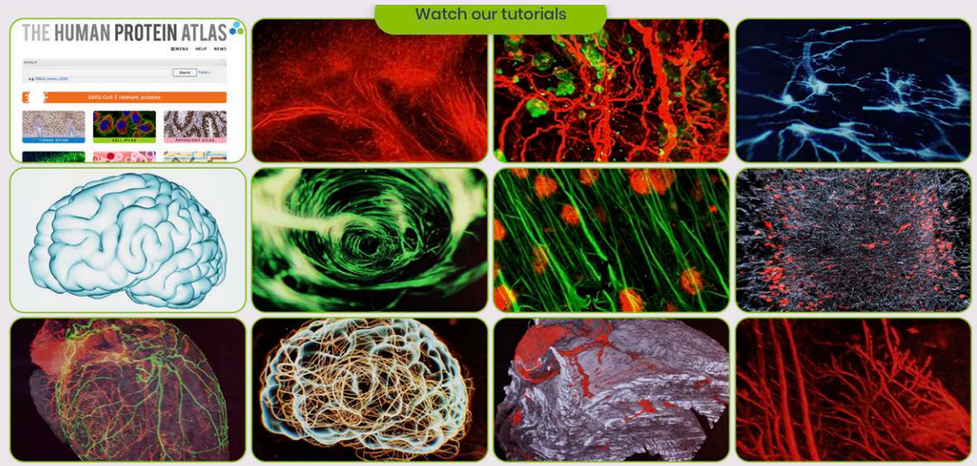
When proteins don't function properly, disease results. Follow these journeys into brain regions afflicted by various neurological diseases.



https://hpajourney.proteinatlas.org

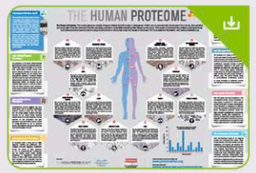
The HPA tutorial videos

A number of tutorial videos have been produced to show different aspects of the Human Protein Atlas and its content. These can be accessed at the HPA video channel.
https://www.proteinatlas.org/learn/videos

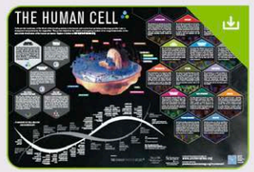


HPA posters

In partnership with Science, HPA created four visually stunning educational posters about different aspects of the Human Protein Atlas. Flip through them here and click on the links to download a PDF copy.
https://www.proteinatlas.org/news/press+room#material

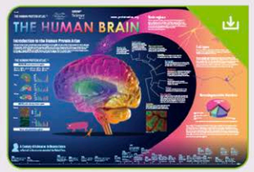


The Tissue Atlas (2015)

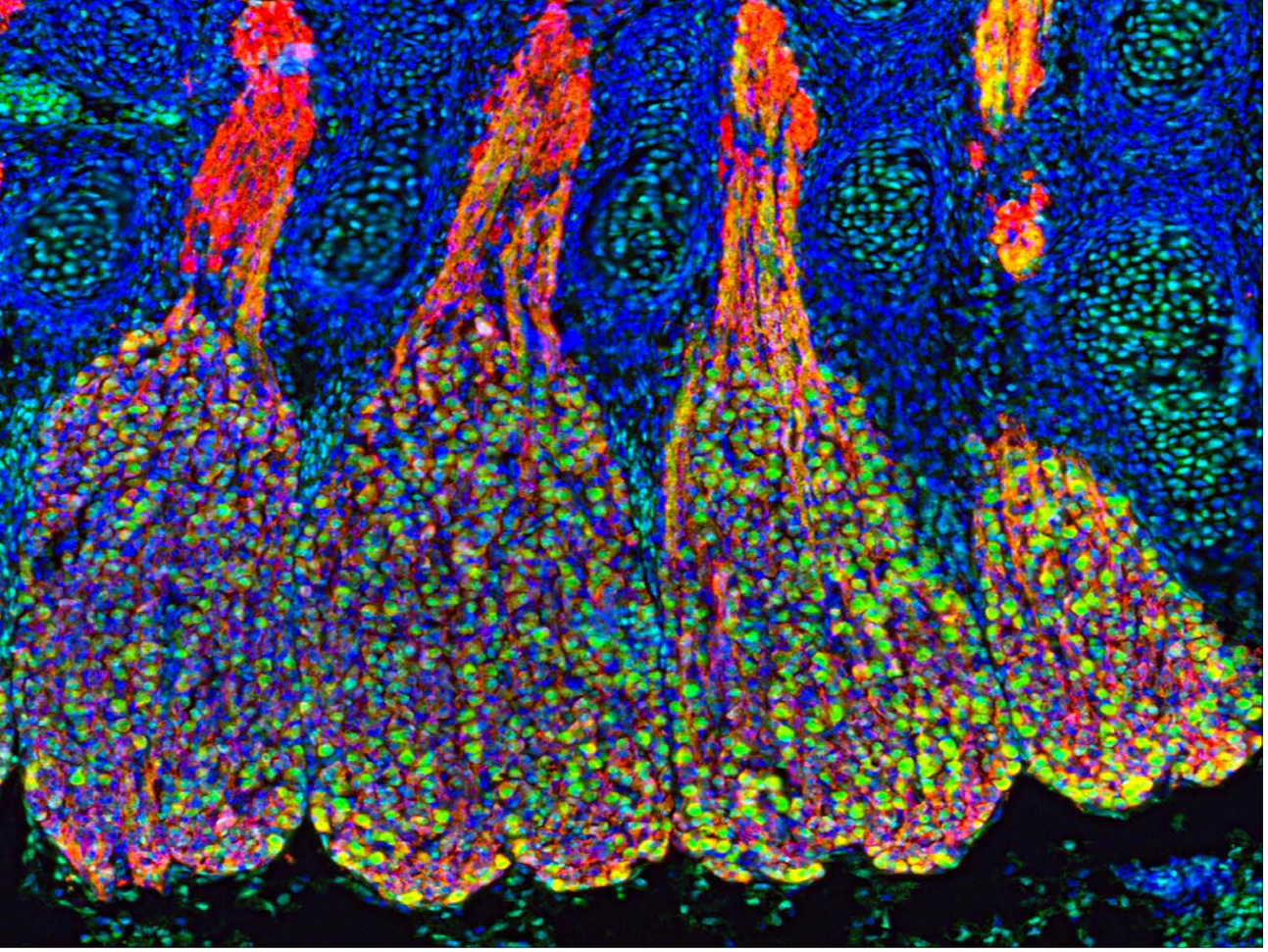


The Cell Atlas (2017)

The Blood Atlas (2019)



The Brain Atlas (2019)



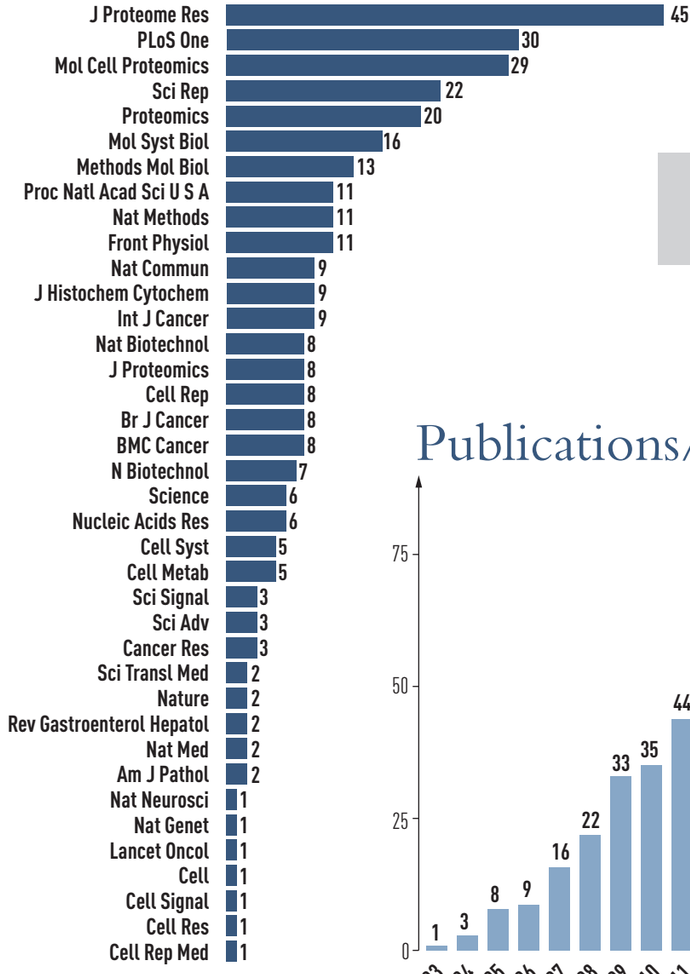
Mapping the human brain

Publications

The HPA consortium has published more than 700 peer-revied publications since the start of the program (https://www.proteinatlas.org/about/publications). Almost all of these involves collaboration across several of the universities in Sweden. More than half of the publications has at least one co-author from abroad.

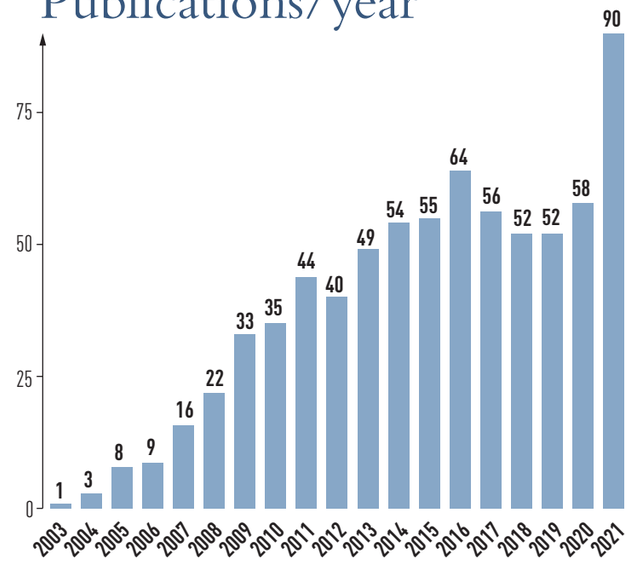
More than 100 papers are published in journals with an impact factor larger than 10. The flag ship paper by Uhlen et al in 2015 describing the Tissue Atlas is now one of the most cited scientific papers from Europe in the last decade with more than 6,000 citations from external groups.

Journals (selected)



HPA consortium

Publications/year



People

The Human Protein Atlas is the result of contributions from many researchers, each providing data and input to the different parts of the database. Below is a partial list (In alphabetical order) of more than 600 researchers who contributed to the creation of the atlas.

The HPA consortium at different times

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The new Human Disease Blood Atlas

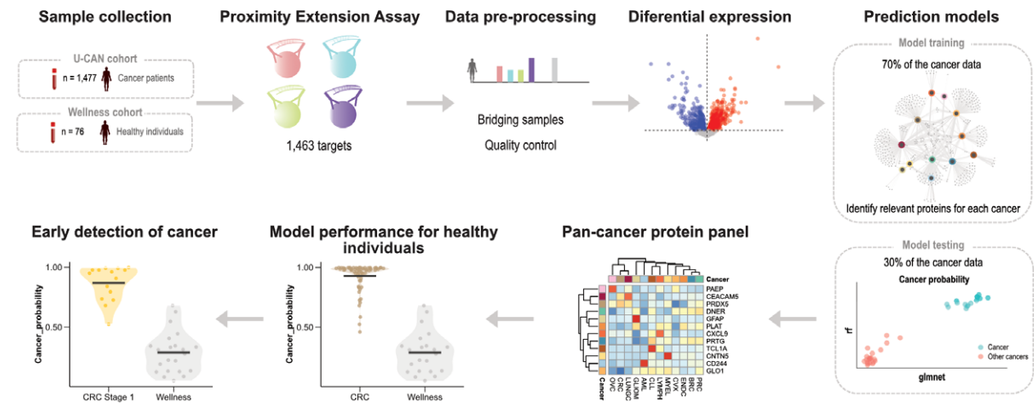
Vision: Provide an open access resource called the Human Disease Blood Atlas for comprehensive and accurate protein levels in blood covering various diseases.

Objectives: (I) Analyze with next generation blood profiling more than 100 major diseases with up to hundred patients each, altogether between 10,000 and 20,000 samples. (II) To provide the most extensive blood analysis ever done, presented to the research community with limited clinical metadata.

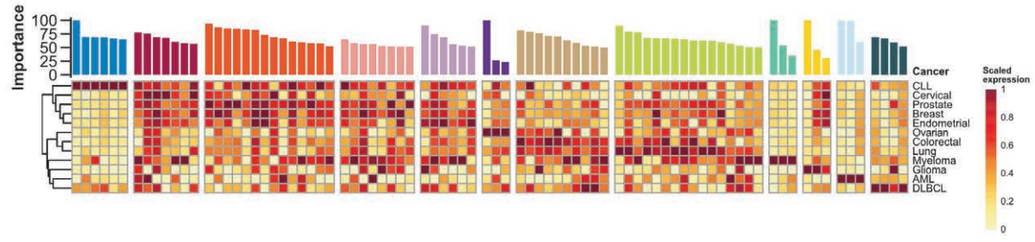
Background: A comprehensive characterization of the blood proteome profiles with various diseases in patients can contribute to a better understanding of the disease etiology, resulting in earlier diagnosis, risk stratification and better monitoring of the disease progression. Precision Medicine thus aims to allow for an individualized diagnosis, treatment and monitoring of patients, including the use of molecular tools such as genomics, proteomics and metabolomics.

Status: A novel strategy for pan-disease analysis has been developed in which the plasma profiles of patients with many different diseases are compared to find disease-specific signatures Next Generation Blood Profiling has been used combining antibody-based proximity extension assay with next generation sequencing to allow the exploration of the protein concentrations in blood from patients with different diseases. AI-based disease prediction models were used to identify a panel of proteins associated with each of the diseases. The primary aim of the protein panel is to distinguish plasma protein profiles from different diseases, such as cancers, and this panel has subsequently been used to also explore the differences in plasma signatures vis-a-vis healthy individuals and patients with early disease.

Resource: All data will be published as part of a new Disease Blood Atlas at the Human Protein Atlas (www.proteinatlas.org). The first version of the Disease Blood Atlas with a focus on cancers will be launched in December 2022.



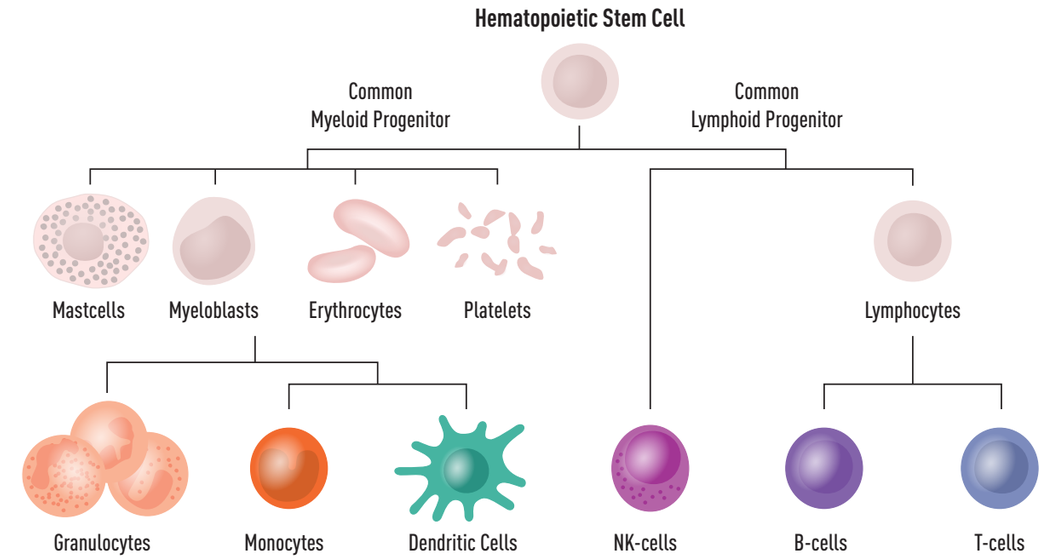
The pipe-line for the novel program to characterize the protein profiles in blood across all major diseases

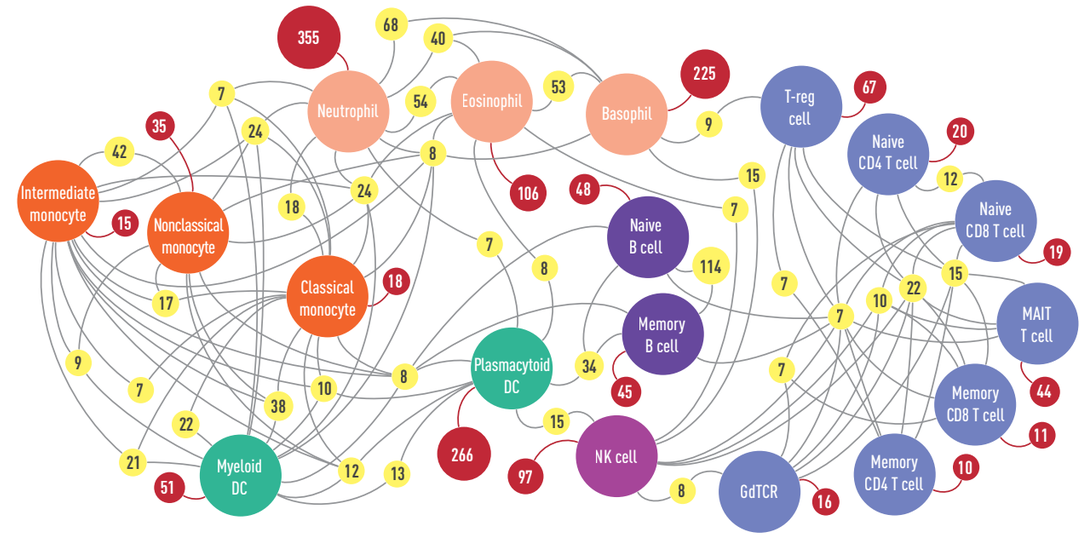


AI-based model for prediction of important proteins in the field of pan-cancer precision medicine

What have we learned about the building-blocks of humans

- Human beings consist of approximately 30 trillion ($30x10^{13}$) cells
- Each cell contains approximately 3 billion base pairs (in two copies) encoding approximately 20,000 protein-coding genes
- The protein-coding parts correspond to only 1,1% of the whole genome
- Proteins are responsible for the majority of all biological functions, including:
  - -Catalysis (enzymes)
  - -Defence (immune proteins)
  - -Structure
  - -Signalling
  - -Reproduction
  - -Cell growth and renewal
- 10% of the proteins are "house-keeping" and thus needed in all dividing cells
- Only 15% of the proteins are "specific" (tissue and single cell enriched)
- Testis and brain contain most tissue-enriched proteins
- 13% of proteins belong to the "secretome", but only one third of these are transported to the blood
- With a simple sample using minute amounts of blood, thousands of proteins can be analyzed in parallel
- Humans have a unique blood protein "fingerprint" which means that all of us have a stable individual profile that differs from others





The immune cell specific proteins according to Uhlen et al, Science (2019).

Start-ups related to the program

The HPA program has been involved in altogether 12 start-ups. These companies range from consumer-based reagent companies to the development of drugs and running human clinical trials. In addition, the HPA program has been closely involved in many ways with a start-up from Uppsala (Olink), which is now listed on NASDAQ (New York).

Start-up	Founded	Description	Status
Atlas Antibodies	2006	50,000 products, >100 MSEK annual sales, 98% export	Highly profitable
Atlas Therapeutics	2006	Sold to Alligator Bioscience	Public (Nasdaq OMX, Stockholm)
Atlas Intressenter	2010	Holding company, 125 researchers	Sold to Patricia 2022
Abclon (South Korea)	2010	Therapeutic antibodies (in clinical trials)	Public (COSDAQ, South Korea)
Antibodypedia	2013	Open access resource for antibodies.	Profitable, 4 million entries
ScandiBio Therapeutics	2017	AI-based drugs for metabolic diseases.	Clinical trials on-going
ScandiEdge Therapeutics	2017	Medical chemistry for liver diseases	4 candidate drugs developed
Amylonix	2018	Biological drugs for neurodegenerative diseases (Alzheimer, Parkinson)	Several patent applications filed
ProteomEdge	2019	Protein diagnostics using targeted mass spectrometry	Several patent applications filed
Mindforce Game Lab	2020	Software apps for health	Clinical trials on-going
A05 Diagnostics	2021	COVID-19 diagnostics	>1,5 million tests for FoHM
Zytox	2022	Bispecific biopharmaceuticals	Pre-clinical stage

The location of some of the start-ups from the HPA consortium

Acknowledgments

We acknowledge all of the HPA teams for their hard work during the 20 years since the start of the HPA effort. More than 1,500 person-years have been invested to create this open-access public database, which has over 400,000 visitors per month from more than 150 countries.

We are grateful to the Knut and Alice Wallenberg Foundation for being the main funder of the HPA program.

About the Knut and Alice Wallenberg Foundation
The Knut and Alice Wallenberg Foundation is the largest private financier of research in Sweden and also one of the largest in Europe. The foundation's aim is to benefit Sweden by supporting basic research and education, mainly in medicine, technology, and the natural sciences. The foundation can also initiate grants for strategic projects and scholarship programs. For more information, see kaw.wallenberg.org.

About the Science for Life Laboratory
Science for Life Laboratory (SciLifeLab) is a research institution for the advancement of molecular biosciences in Sweden. SciLifeLab started out in 2010 as a joint effort between four universities: Karolinska Institutet, KTH Royal Institute of Technology, Stockholm University, and Uppsala University. The center provides access to a variety of advanced infrastructures in life science for thousands of researchers, creating a unique environment for health and environmental research at the highest level. For more information, see www.scilifelab.se.

About Karolinska Institutet
The vision of Karolinska Institutet (KI) is to advance knowledge about life and strive toward better health for all. As a university, KI is Sweden's largest center of medical academic research and offers the country's widest range of medical courses and programs. Since 1901, the Nobel Assembly at Karolinska Institutet has selected the Nobel laureates in Physiology or Medicine. For more information, see ki.se/en.

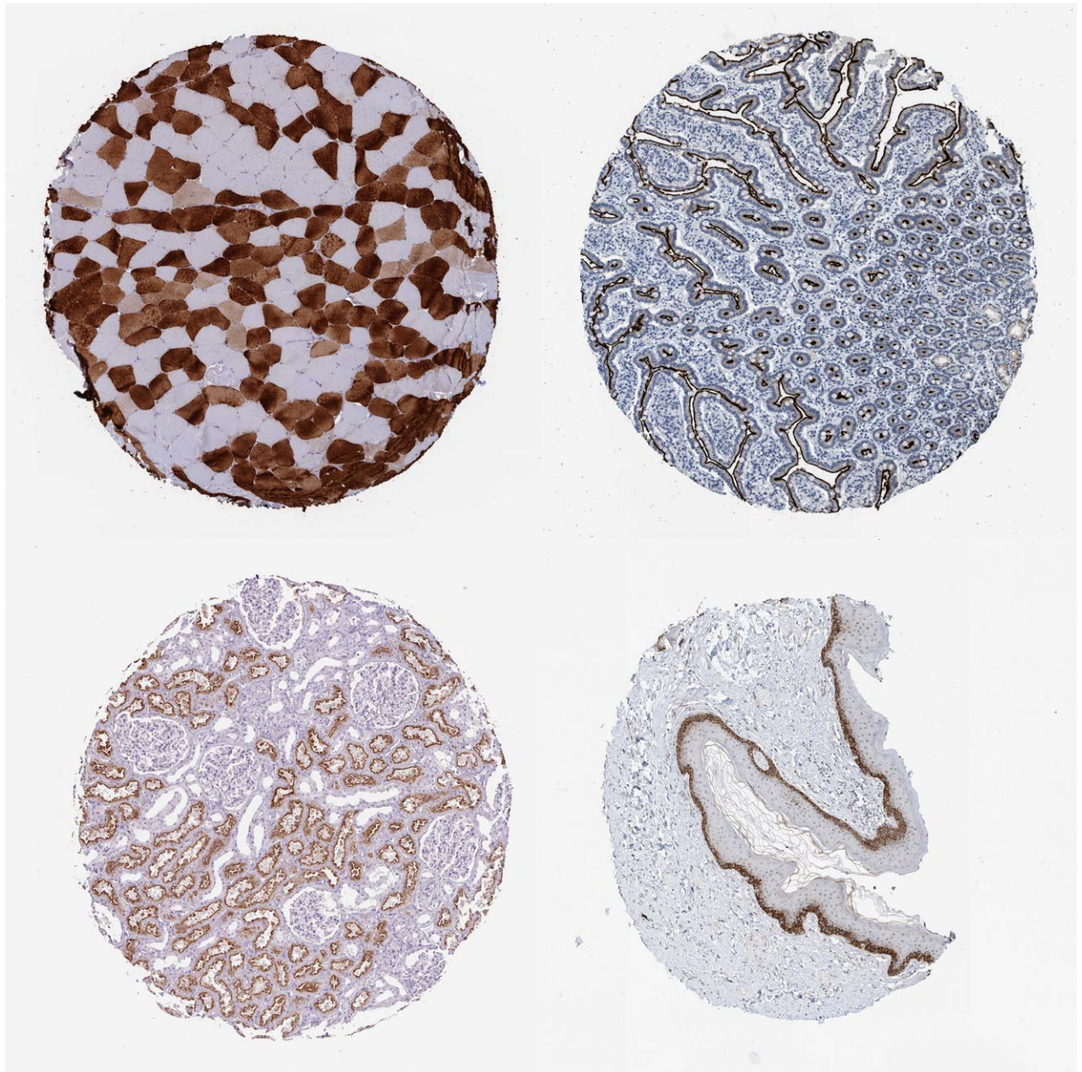
About KTH Royal Institute of Technology
Since its founding in 1827, KTH Royal Institute of Technology in Stockholm has grown to become Sweden's largest technical research and learning institution. For more information, see www.kth.se/en.

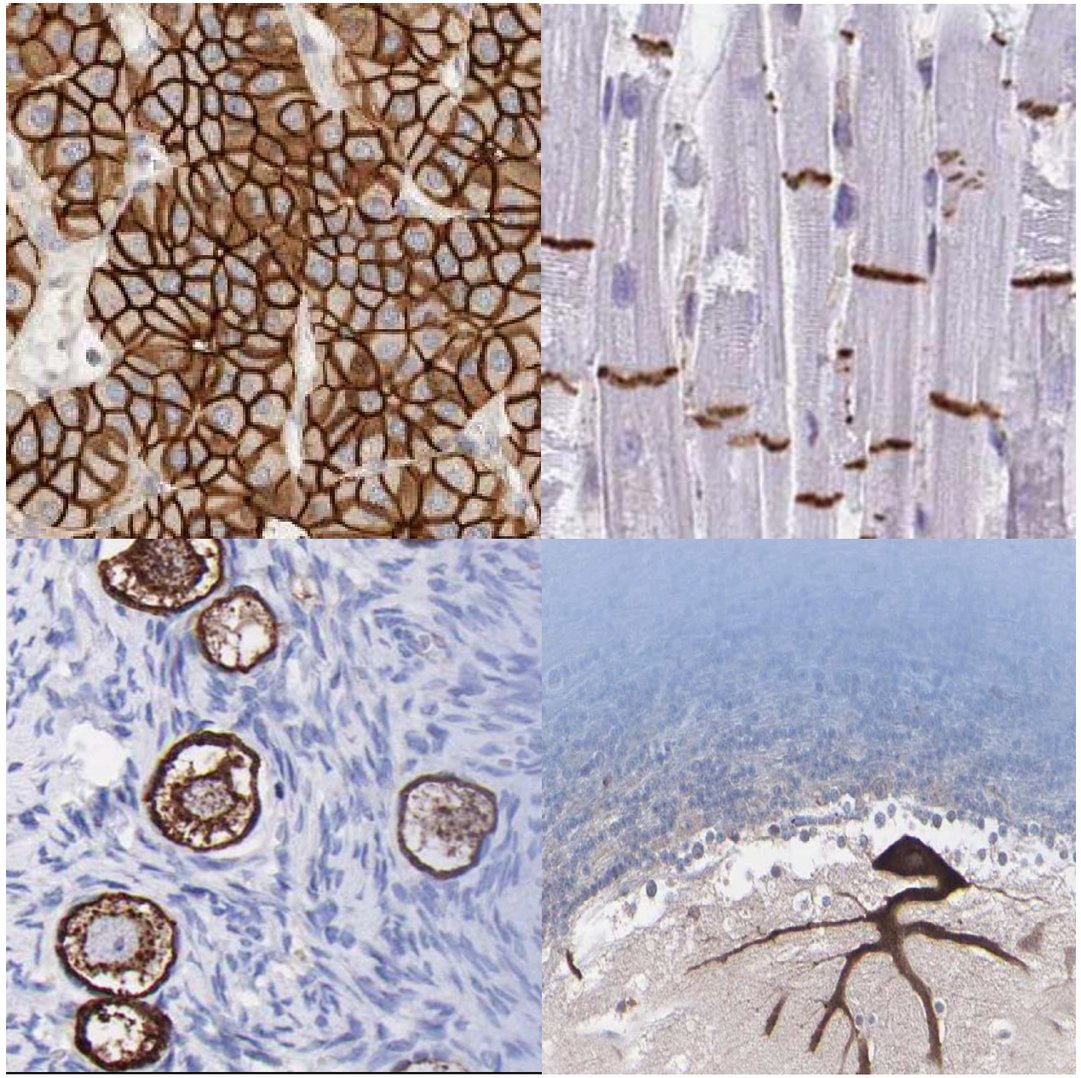
About Uppsala University
Uppsala University is the Nordic region's oldest university—founded in 1477—and is divided into three disciplinary domains: humanities and social sciences, medicine and pharmacy, and science and technology. These in turn comprise nine faculties and nearly 50 departments in total. For more information, see www.uu.se/en.

About Elixir
ELIXIR unites Europe's leading life science organisations in managing and safeguarding the increasing volume of data being generated by publicly funded research. It coordinates, integrates and sustains bioinformatics resources across its member states and enables users in academia and industry to access services that are vital for their research.

The Human Protein Atlas project is funded by the Knut & Alice Wallenberg foundation.

Human tissue stained with HPA antibodies






Pancreas
PRDX4
Endometrium
COL4A2
Colon
RBL1
Tonsil
PTGES
Liver
PON3
Endometrium
TAGLN
Colon
TMEM192
Skeletal muscle
STBD1
Smooth muscle
SYNM
Fallopian tube
PGR
Parathyroid gland
PTH
Hypothalamus
AVP
Esophagus
SCEL
Kidney
SLC13A3
Cerebellum
SNCG
Hair follicles
TYR
Testis
PTN
Stomach
POLB
Kidney
PODXL
Skin
SFN
Epididymis
SMTN
Testis
SGO2
Hair follicles
DSC1