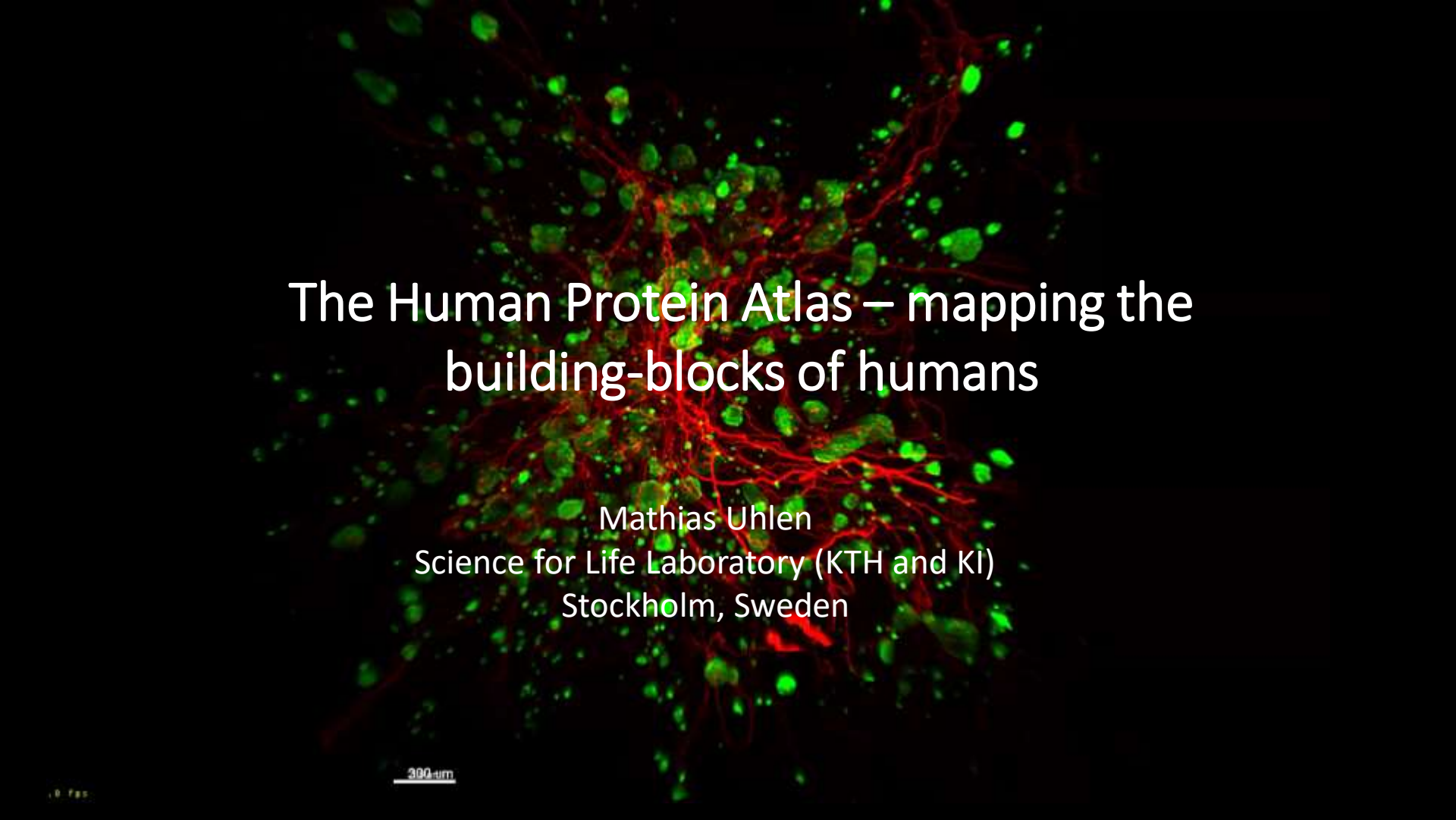


The Human Protein Atlas – mapping the building-blocks of humans

Mathias Uhlen
Science for Life Laboratory (KTH and KI)
Stockholm, Sweden

Disclaimer

- 20 start-up companies
- Atlas antibodies, Affibody, Abclon, ScandiBio Therapeutics
- AstraZeneca, GE Health

- Professor KTH, KI and DTU
- Director of Human Protein Atlas
- Founding Director of Science for Life Laboratory
- Member of the Royal Academy of Science (Sweden)
- Member of the National Academy of Engineering (USA)
- President of the European Federation of Biotechnology

Scientific mapping

Century	Field
18th	Biology
19th	Chemistry
20th	Physics
21st	Medicine

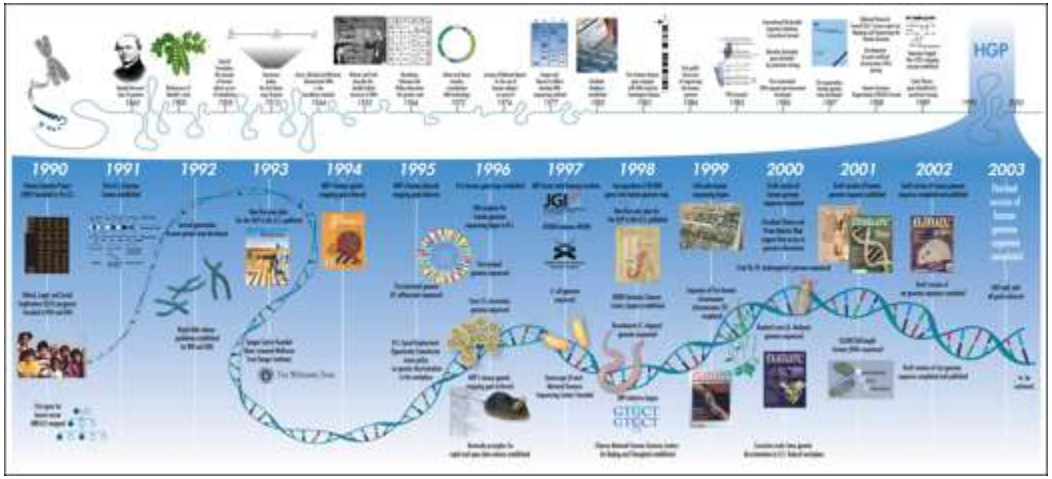
Linneus

Berzelius

Periodic Table (chemistry)

- Dimitri Mendeleev
- 150 year anniversary
- Prediction of missing elements
- 118 elements discovered (2019)

The human genome (2003)



- Few protein-coding genes (23,000)
- Blue-print for human biology and diseases

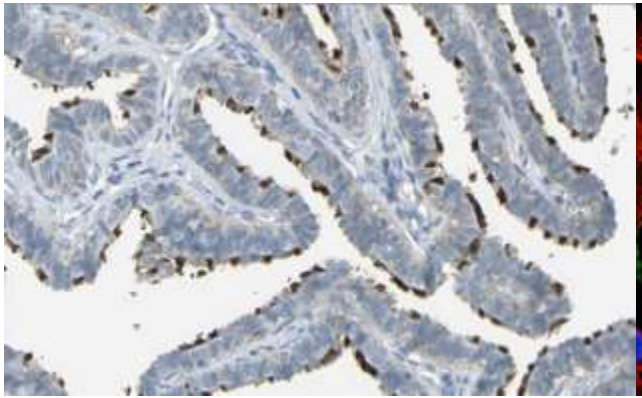
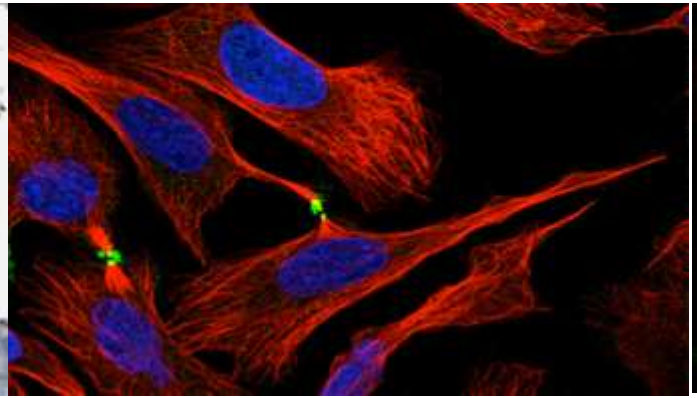
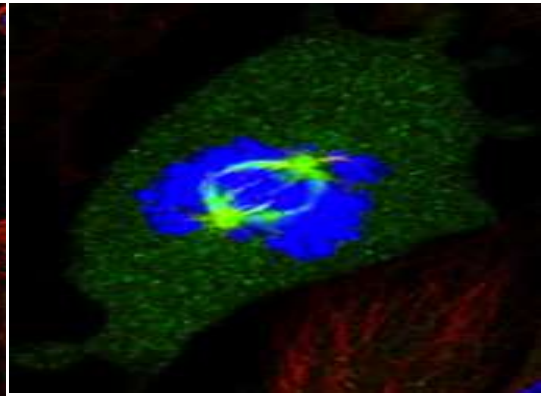
The human proteome – making a ”periodic table” of the proteins

- Proteins – the building blocks of human biology
- Targets for all pharmaceutical drugs
- Targets for future precision medicine efforts

- What are the building-blocks of tissues and organs ?
- What is the building-blocks of the cell ?
- What are the targets for future drugs and diagnostics ?

Content

1. The Human Protein Atlas – an update
2. The Human Proteome – an update
3. The human Secretome –a resource of secreted proteins
4. Precision medicine (wellness profiling)
5. Biologicals for drug treatment

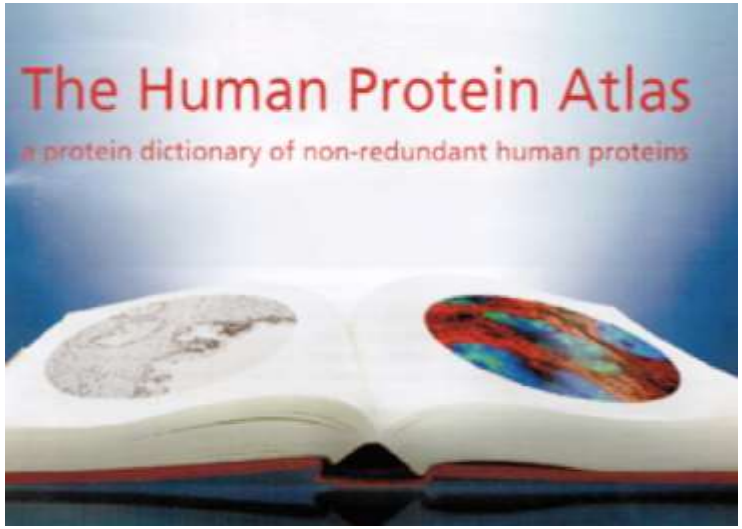




1.

The Human Protein Atlas –

an update

The Human Protein Atlas



- Map of all human proteins in cells, tissues and organs (including cancer)
- Open knowledge resource for all researchers in academia and industry
- Started in 2003
- Funded by Wallenberg Foundation

THE HUMAN PROTEIN ATLAS

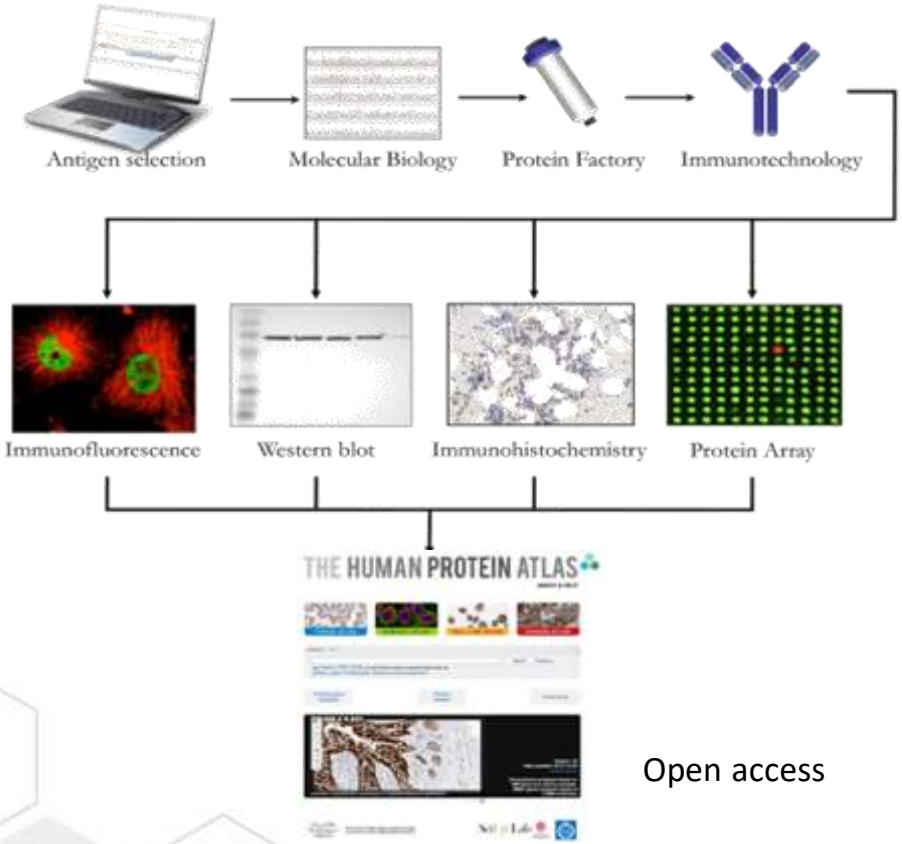
Knut och Alice Wallenbergs Stiftelse

Sweden and Asia

- **SciLifeLab Solna (KTH)**
- **AlbaNova (KTH)**
- **Rudbeck (Uppsala)**
- **Neuoscience (Karolinska)**
- **Systems biology (Chalmers)**

- **South Korea (production of antibodies)**
- **China (transcriptomics and antibodies)**
- **India (pathologists for annotation)**

Research factory

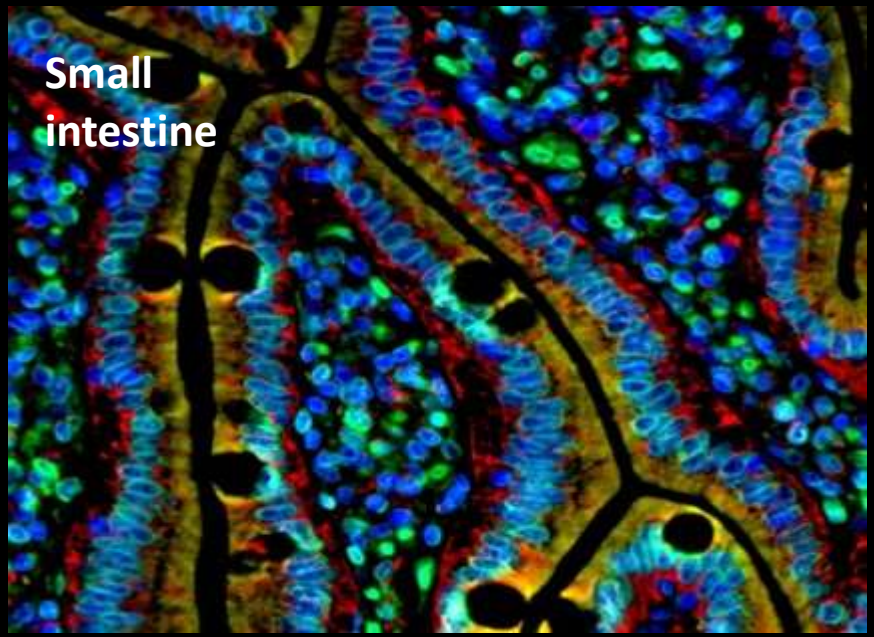


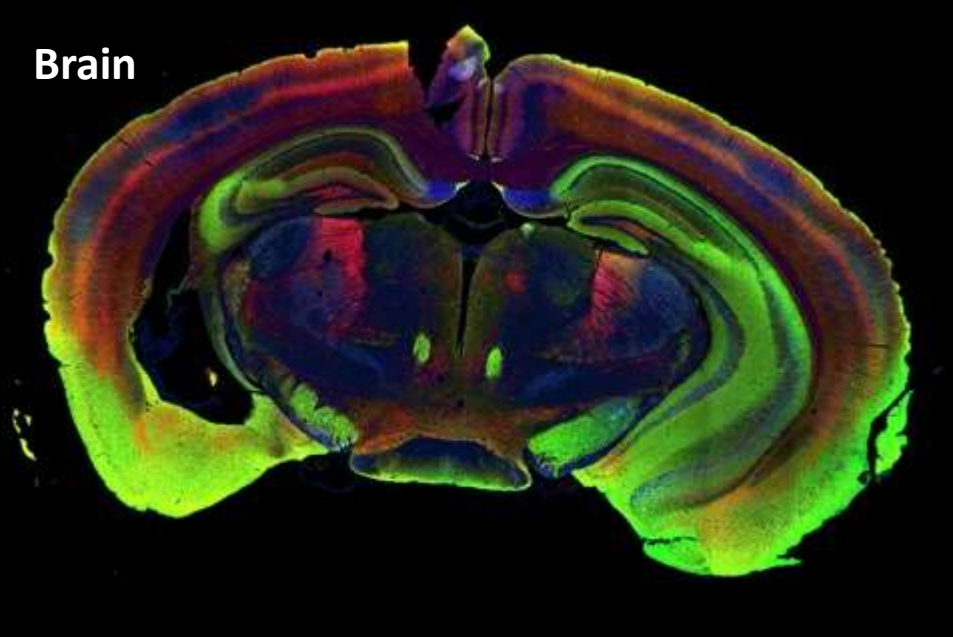
- **60,000 recombinant proteins** (produced in E.coli and CHO cells)
- **55,000 antibodies** (affinity-purified on the antigen)
- 21,000 validated antibodies for bioimaging of tissues and cells
- Integration with transcriptomics

Open access

THE HUMAN PROTEIN ATLAS

More than 10 million images





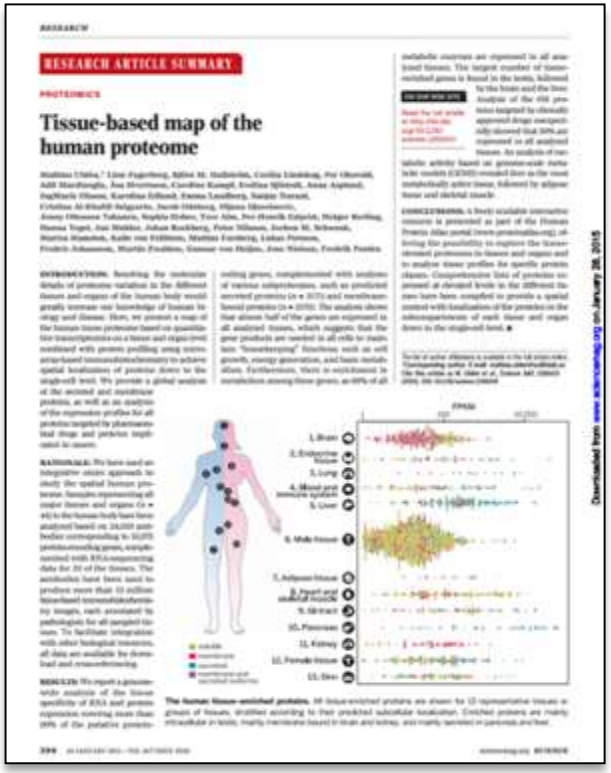
Antibody-based bioimaging - ”in-house” generation of 55,000 antibodies

Tissue Atlas (2015)

Science
AAAS

Uhlen et al (2015)
”Tissue-based map of the human proteome”
Science 347: 394

More than 3000 citations (Google Scholar)



RESEARCH ARTICLE SUMMARY

PROTEOMICS

Tissue-based map of the human proteome

Caroline Kampf

Cecilia Lindskog

Fredrik Ponten

- Single cell resolution
- Context of neighboring cells
- In vivo analysis (tissues)

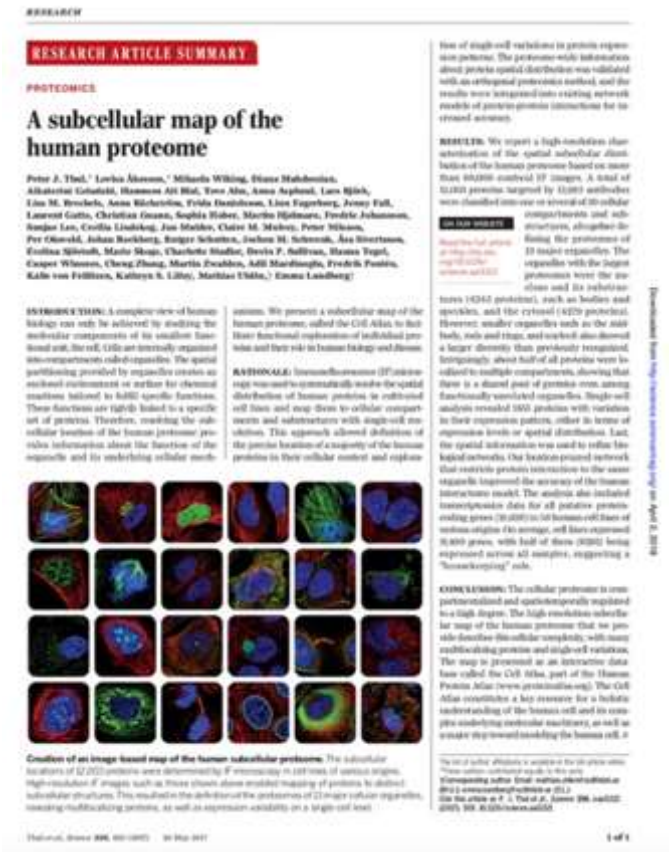
THE HUMAN PROTEIN ATLAS

Cell Atlas - Subcellular profiling (2017)

Science
AAAS

Thul et al (2017) ”A subcellular map of the human proteome” Science 347: 394

More than 400 citations (Google Scholar)



RESEARCH ARTICLE SUMMARY

PROTEOMICS

A subcellular map of the human proteome

Peter J. Thul,† Lovisa Åkesson,† Mikaela Wiking, Diana Mahdessian, Aikaterini Geladaki, Hammou Ait Blal, Tove Alm, Anna Asplund, Lars Björk, Lisa M. Breckels, Anna Bäckström, Frida Danielsson, Linn Fagerberg, Jenny Fall, Laurent Gatto, Christian Gnann, Sophia Hober, Martin Hjelmare, Fredrik Johansson, Jungyun Lee, Cecilia Lindskog, Jan Mulder, Claire M. Mulvey, Peter Nilsson, Per Oksvold, Johan Rockberg, Rutger Schutten, Jochen M. Schwenk, Åsa Sivertsson, Evelina Sjöstedt, Marie Skogs, Charlotte Stadler, Devin P. Sullivan, Hanna Tegel, Casper Winsnes, Cheng Zhang, Martin Zwahlen, Adil Mardinoglu, Fredrik Ponten, Kalle von Feilitzen, Kathryn S. Lilley, Mathias Uhlén,‡ Emma Lundberg‡

INTRODUCTION: A complete view of human biology can only be achieved by studying the molecular components of its smallest functional unit, the cell. Cells are internally organized into compartments called organelles. The spatial partitioning provided by organelles creates an enclosed environment or surface for chemical reactions tailored to fulfill specific functions. These functions are tightly linked to a specific set of proteins. Therefore, resolving the subcellular location of the human proteome provides vital information about the functions of the organelle and its underlying cellular mech-

anisms. We present a subcellular map of the human proteome, called the Cell Atlas, to facilitate functional exploration of individual proteins and their role in human biology and disease.

RATIONALE: Immunofluorescence (IF) microscopy was used to systematically resolve the spatial distribution of human proteins in cultured cell lines and map them to cellular compartments and substructures with single-cell resolution. This approach allowed definition of the precise location of a majority of the human proteins in their cellular context and explora-

tion of single-cell variations in protein expression patterns. The proteome-wide information about protein spatial distribution was validated with an orthogonal proteomics method, and the results were integrated into existing network models of protein-protein interactions for increased accuracy.

RESULTS: We report a high-resolution characterization of the spatial subcellular distribution of the human proteome based on more than 400,000 confocal IF images. A total of 12,003 proteins targeted by 13,993 antibodies were classified into one or several of 30 cellular

ON OUR WEBSITE

compartments and substructures, altogether defining the proteome of 10 major organelles. The organelles with the largest proteomes were the nucleus and its substructures (4,042 proteins), such as bodies and speckles, and the cytosol (4,029 proteins). However, smaller organelles such as the mitochondria, cilia and rings, and nucleoli also showed a larger diversity than previously recognized. Surprisingly, about half of all proteins were localized to multiple compartments, showing that there is a shared pool of proteins even among functionally specialized organelles. Single-cell analysis revealed 1,661 proteins with variation in their expression pattern, either in terms of expression levels or spatial distribution. Last, the spatial information was used to refine biological networks. Our location-primed network that controls protein interaction to the same organelle improved the accuracy of the human interactome model. The analysis also included transcriptomics data for all putative protein-coding genes (20,050) in 50 human cell lines of various origin. On average, cell lines expressed 9,400 genes, with half of them (4,682) being expressed across all samples, suggesting a "housekeeping" role.

CONCLUSION: The cellular proteome is compartmentalized and spatiotemporally regulated to a high degree. The high-resolution subcellular map of the human proteome that we provide describes this cellular complexity, with many multilocalizing proteins and single-cell variations. The map is presented as an interactive database called the Cell Atlas, part of the Human Protein Atlas (www.proteinatlas.org). The Cell Atlas constitutes a key resource for a holistic understanding of the human cell and its complex underlying molecular machinery, as well as a major step toward modeling the human cell.

Creation of an image-based map of the human subcellular proteome. The subcellular locations of 12,003 proteins were determined by IF microscopy in cell lines of various origins. High-resolution IF images such as those shown above enabled mapping of proteins to distinct subcellular structures. This resulted in the definition of the proteomes of 13 major cellular organelles, revealing multilocalizing proteins, as well as expression variability on a single-cell level.

Downloaded from http://science.sciencemag.org/ on April 2, 2018

Emma Lundberg

Peter Thul

- Subcellular resolution (confocal)
- Single cell variation

THE HUMAN PROTEIN ATLAS

Pathology Atlas (2017)

Science
AAAS

Uhlen et al (2017)
"A pathology atlas of human cancer proteomes"
Science 357(6352)

More than 400 citations (Google Scholar)

RESEARCH ARTICLE SUMMARY

HEAD SUBJECT

A pathology atlas of the human cancer transcriptome

Mathias Uhlen *et al.*

INTRODUCTION: Cancer is a leading cause of death worldwide, and there is great need to define the molecular mechanisms driving the development and progression of individual tumors. The Hallmarks of Cancer has provided a framework for a deeper molecular understanding of cancer and the focus so far has been on the genetic alterations in individual cancers, including genome re-arrangements, gene amplifications and specific cancer-driving mutations. Using systems-level approaches, it is now also possible to define downstream effects of individual genetic alterations in a genome-wide manner.

RATIONALE: In our study, we used a systems-level approach to analyze the transcriptome of 17 major cancer types with respect to clinical outcome and based on a genome-wide transcriptomics analysis of approximately 8,000 individual patients with clinical metadata. The study was made possible through the availability of large open-access knowledge-based efforts, such as the Cancer Genome Atlas (TCGA) and the Human Protein Atlas (HPA). Here, we used the data to perform a systems-level analysis of 17 major human cancer types describing both inter-individual and inter-tumor variation patterns (Fig.1).

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Read the full article at http://dx.doi.org/10.1126/science.aan2507

RESULTS: The analysis identified candidate prognostic genes associated with clinical outcome for each tumor type, and the results show that a large fraction of cancer protein coding genes are differentially expressed - and in many cases - have an impact on overall patient survival. Systems biology analyses revealed that gene expression of individual tumors within a particular cancer varied considerably, and could exceed the variation observed between distinct cancer types. No general prognostic gene necessary for clinical outcome was applicable to all cancers. Shorter patient survival was generally associated with up-regulation of genes involved in mitosis and cell growth and down-regulation of genes involved in cellular differentiation. The data allowed us to generate personalized genome-scale metabolic models for cancer patients to identify key genes involved in tumor growth. In addition, tissue-specific genes associated with the "dedifferentiation" of tumor cells and the role of specific cancer testis antigens (CTAs) on a genome-wide scale were explored. For lung and colorectal cancer, a selection of prognostic genes identified by the systems-biology effort were analyzed in independent, prospective cancer cohorts using immunohistochemistry to validate the gene expression patterns at the protein level.

CONCLUSIONS: A Pathology Atlas has been created as part of the Human Protein Atlas program to explore the prognostic role of each protein-coding gene in each cancer type using transcriptomics and antibody-based profiling to provide a standalone resource for cancer precision medicine. The results demonstrate the power of large systematic "big data" efforts utilizing publicly available resources, such as the databases used herein. Using genome-scale metabolic models, we show that cancer patients have widespread metabolic heterogeneity, highlighting the need for precise and personalized medicine for cancer treatment. With its more than 900,000 Kaplan-Meier plots, this resource enables insights concerning the specific involvement of genes in clinical outcome for all the major cancers, paving the way for further in-depth studies incorporating systems-level analyses of cancer. All data presented herein are available in an interactive open-access database (www.proteinatlas.org) to allow for genome-wide exploration of the impact of individual proteins on clinical outcome in major cancer types.

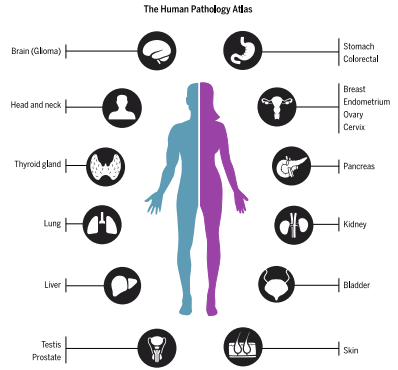


PHOTO: CREDIT GOES HERE AS SHOWN. CREDIT GOES HERE AS SHOWN

Schematic overview of the Human Pathology Atlas. A systems-level approach to analyze the protein-coding genes of 17 different cancer types from approximately 8,000 patients. Results are available in an interactive open-access database (www.proteinatlas.org).

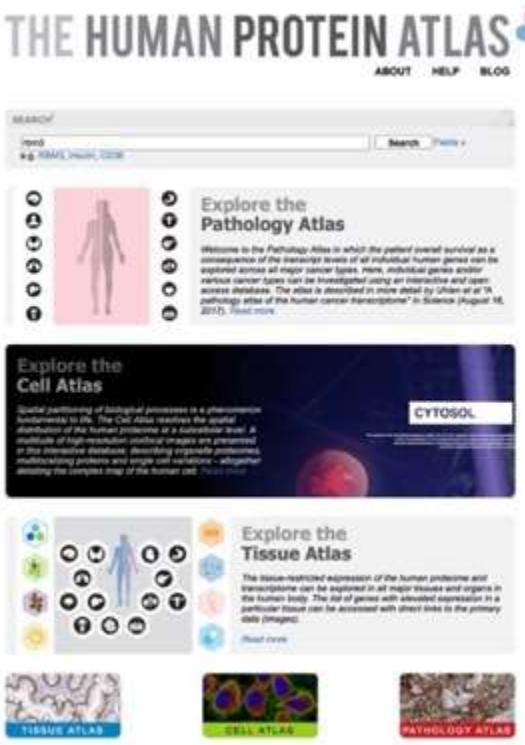
The list of author affiliations is available in the full article online.
*Corresponding author. E-mail: xxxxxxxx@xxxx.au;
Cite this article as X. X. Xxxxxx *et al.*, *Science* XXX, 0000000 (2014). DOI: 10.1126/science.xxxxxxxx

Adil Mardinoglu

Fredrik Ponten

THE HUMAN PROTEIN ATLAS

The Human Protein Atlas three separate parts

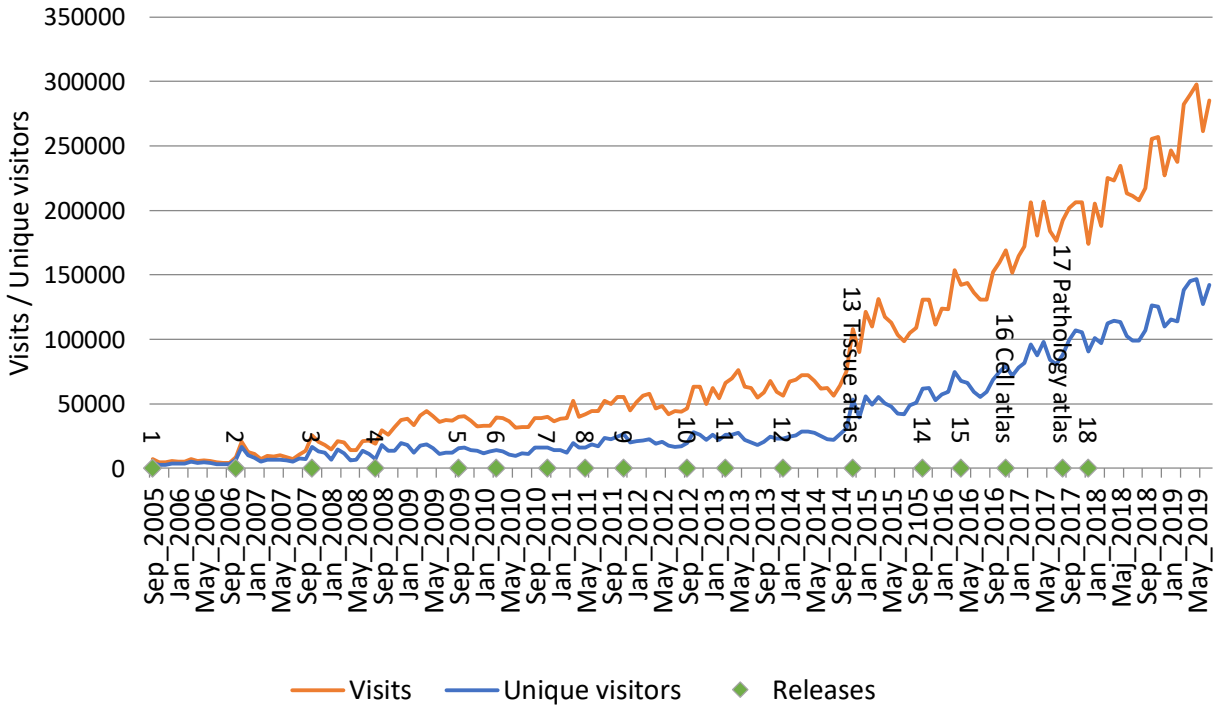


Open access

Atlas	Description	Key publication
Tissue Atlas	Localization of proteins in human tissues and organs	Uhlén et al (2015) *Science*
Cell Atlas	Subcellular localization in single cells	Thul et al (2017) *Science*
Pathology Atlas	Prognostic genes for clinical outcome in cancers	Uhlén et al (2017) *Science*

THE HUMAN PROTEIN ATLAS

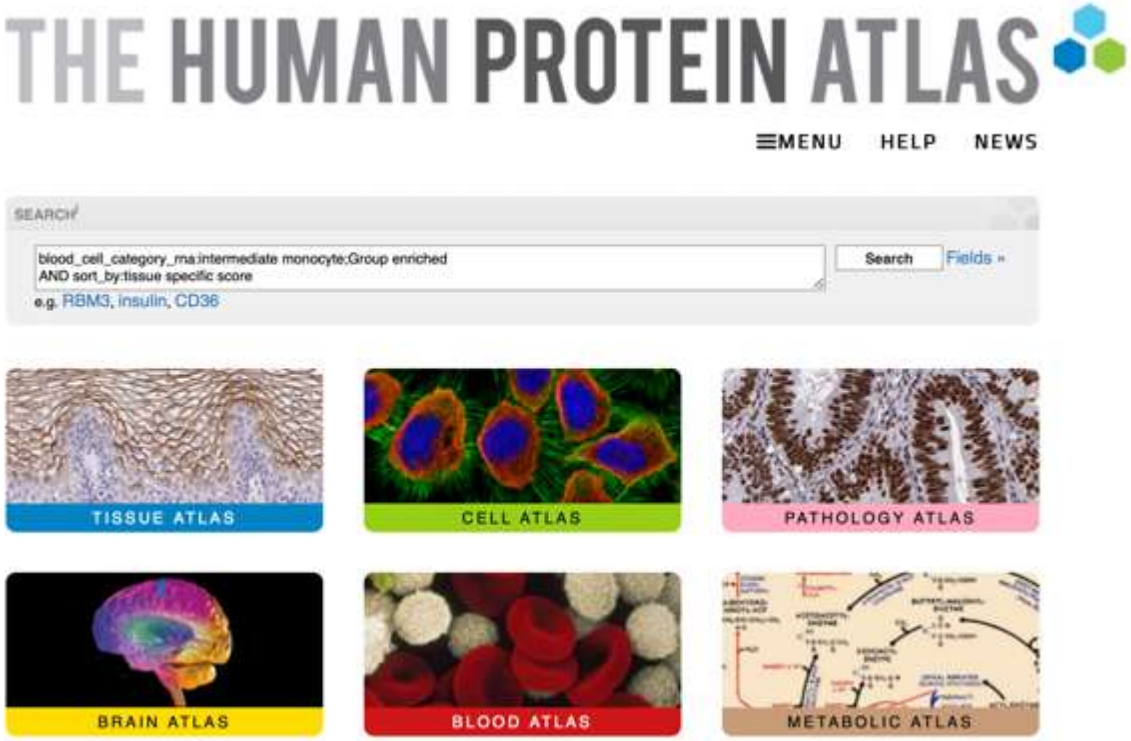
Visitors from academia and industry



- **300,000 visitors per month**
- **10 publications every day citing HPA**

THE HUMAN PROTEIN ATLAS

Human Protein Atlas – new additions



Blood Atlas – what proteins and cells are present in blood

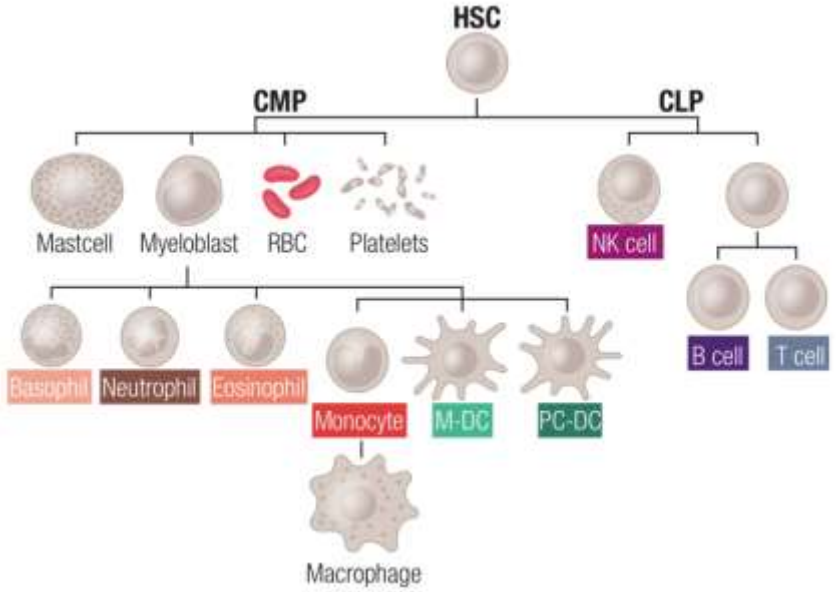
Brain Atlas – what proteins are localized to different regions of the brain

Metabolic Atlas – what metabolic pathways are active in different tissues

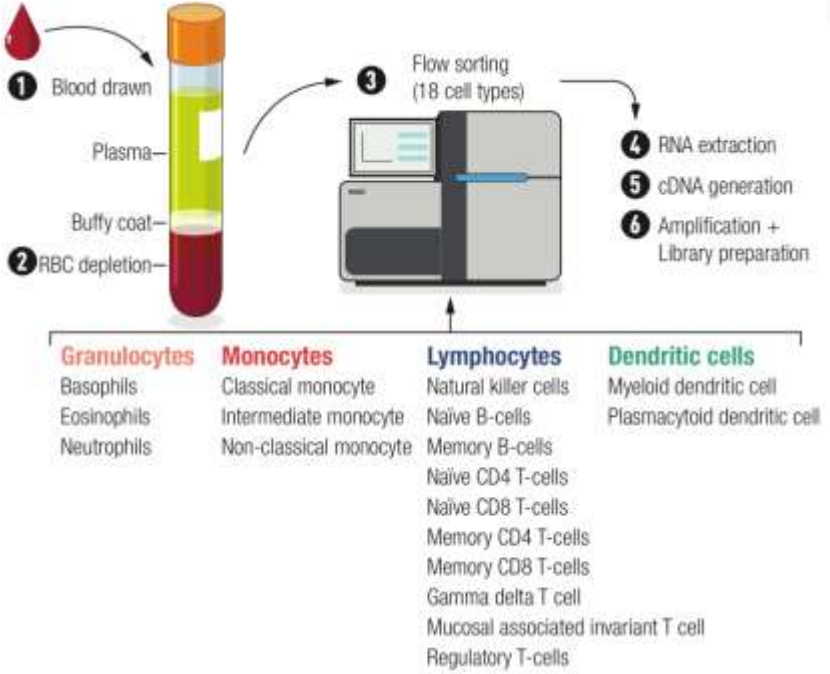
Launched September 5, 2019

Human Blood Atlas

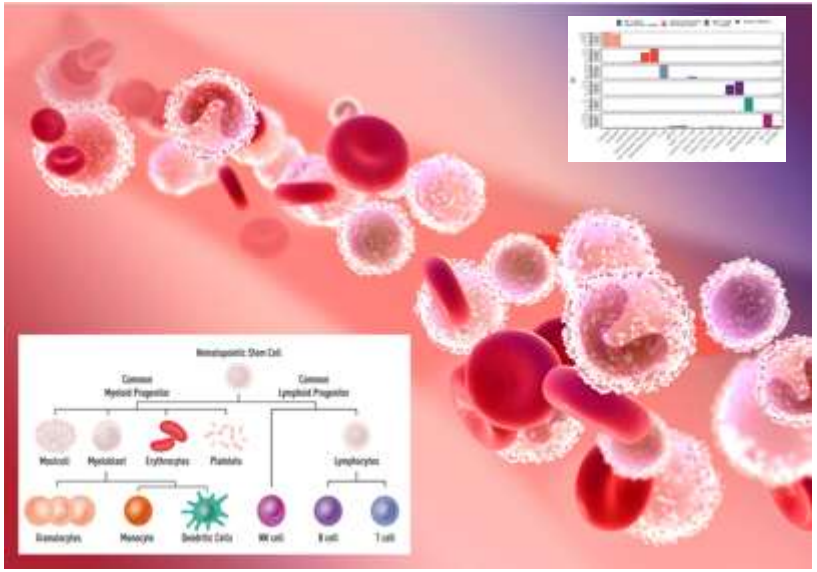
A



B



Map of human blood cell types



- 1,448 blood cell enriched genes
- 271 “specific” for a single cell type

Cell type	Cell lineage	No of cell type enriched genes
Memory B-cell	B-cells	45
Naive B-cell	B-cells	48
Myeloid DC	Dendritic cells	51
Plasmacytoid DC	Dendritic cells	266
Basophil	Granulocytes	225
Eosinophil	Granulocytes	106
Neutrophil	Granulocytes	355
Classical monocyte	Monocytes	18
Intermediate monocyte	Monocytes	15
Non-classical monocyte	Monocytes	35
NK-cell	NK-cells	97
GdTCR	T-cells	16
MAIT T-cell	T-cells	44
Memory CD4 T-cell	T-cells	10
Memory CD8 T-cell	T-cells	11
Naive CD4 T-cell	T-cells	20
Naive CD8 T-cell	T-cells	19
T-reg	T-cells	67

Blood cell map contributors:

- **Linn Fagerberg (KTH)**
- **Petter Brodin (Karolinska)**

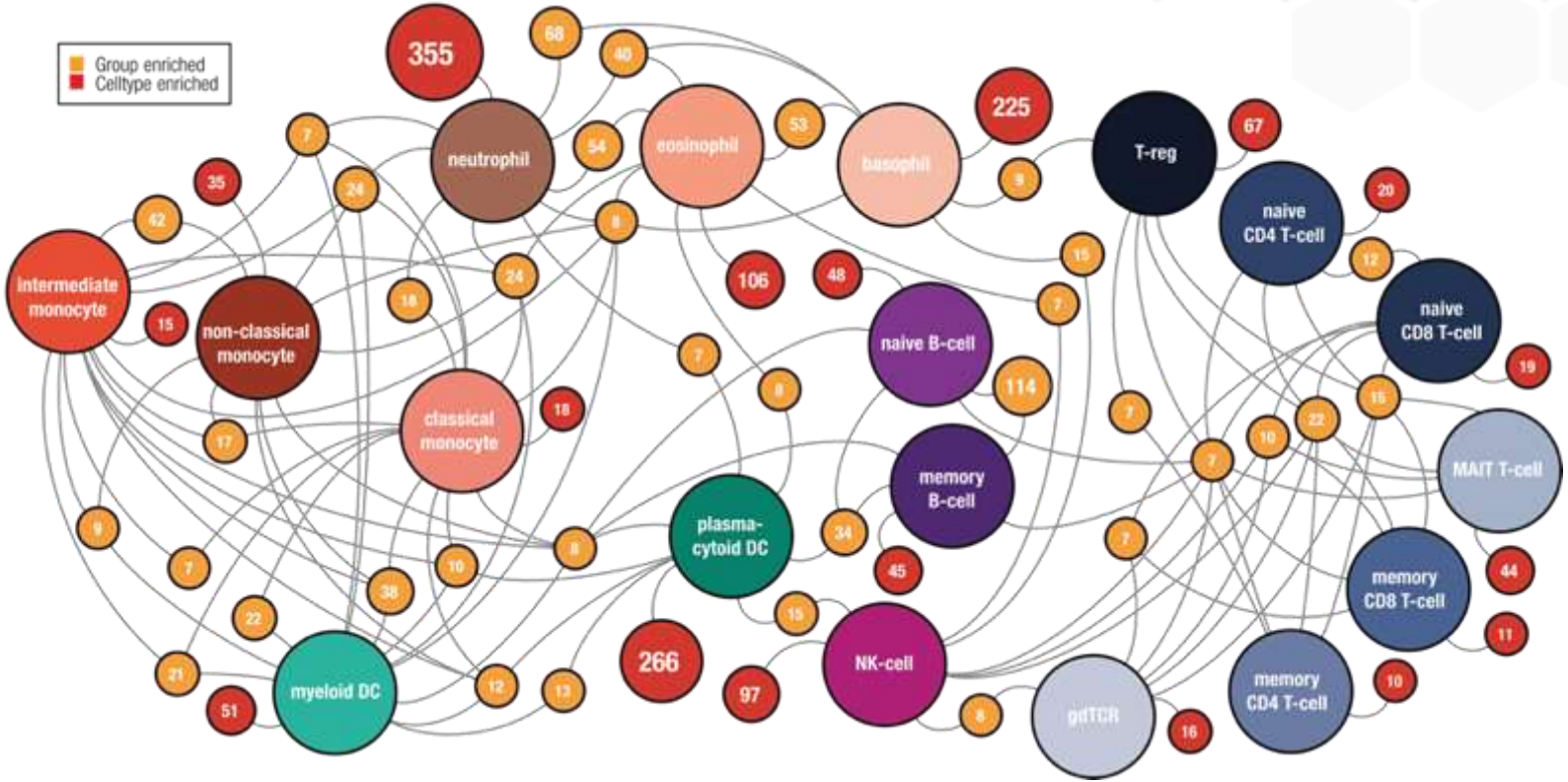
- Max Karlsson (KTH)
- Wen Zhong (KTH)
- Abdellah Tebani (KTH)
- Fredrik Edfors (KTH)
- Åsa Sivertsson (KTH)
- Jacob Odeberg (KI/KTH)
- Martin Zwahlen (KTH)
- Per Oksvold (KTH)
- Kalle von Feilitzen (KTH)

… and many others …

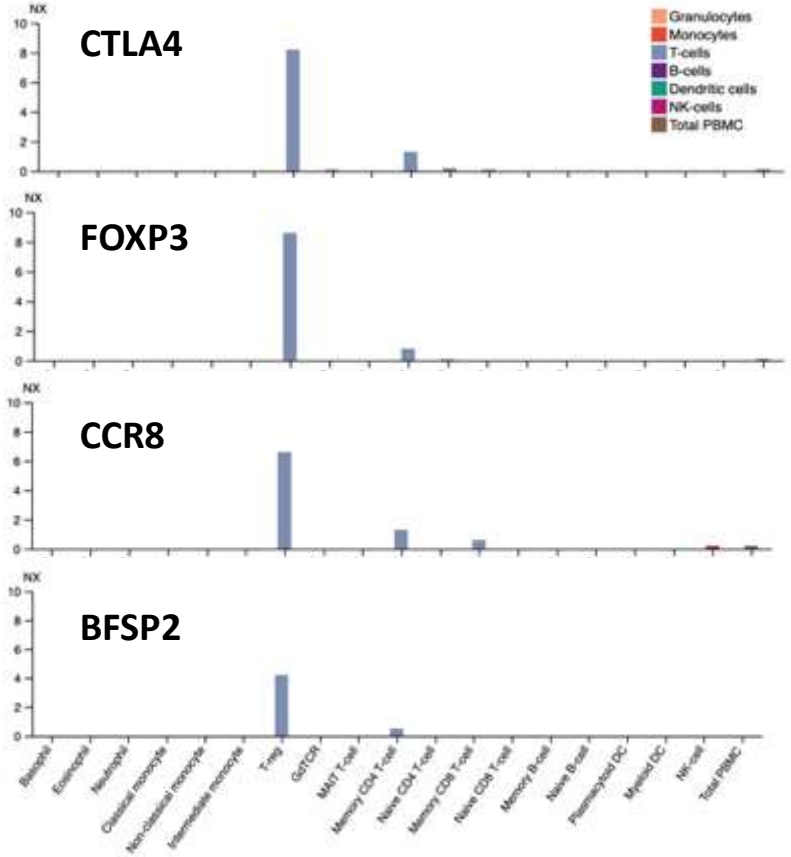
Uhlen et al (2019A), in review

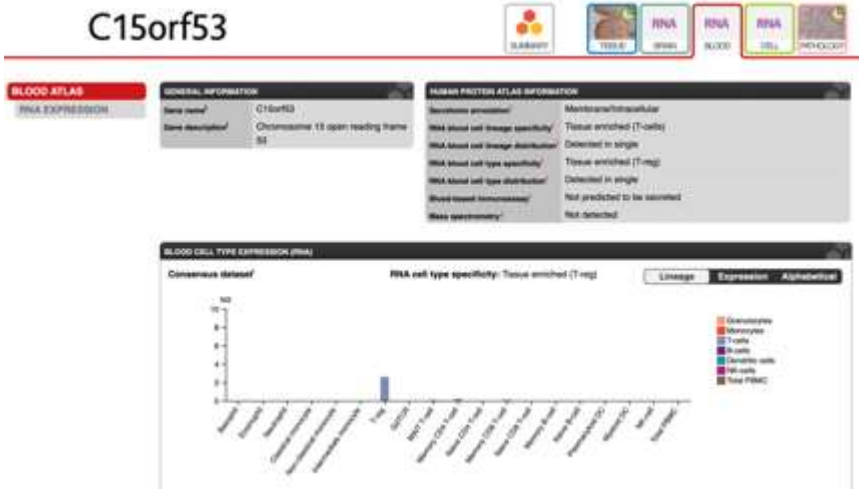
Blood specific genes

Categories based on expression (transcriptomics)



Regulatory T-cell enriched genes





Molecular organization of the brain

→Organ level
→Region level
→Cellular level (cell types)
→Subcellular level (organelle)

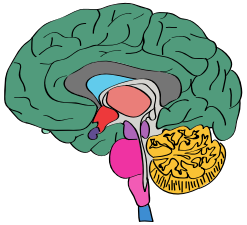
} -Physiology
-Disease

→ Proteomics (antibody-based)
→ Transcriptomics

A mammalian brain atlas

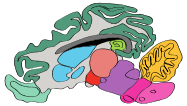
- **Create a map of the gene expression of the mammalian brain**
- **Identify brain relevant genes for in-depth studies**
- **Identify species difference (human, pig and mouse)**

Human



- Samples from 23 regions

Pig



- Samples covering 28 regions (collaboration BGI, China)

Mouse

- Samples covering 17 regions

Brain Atlas contributors:

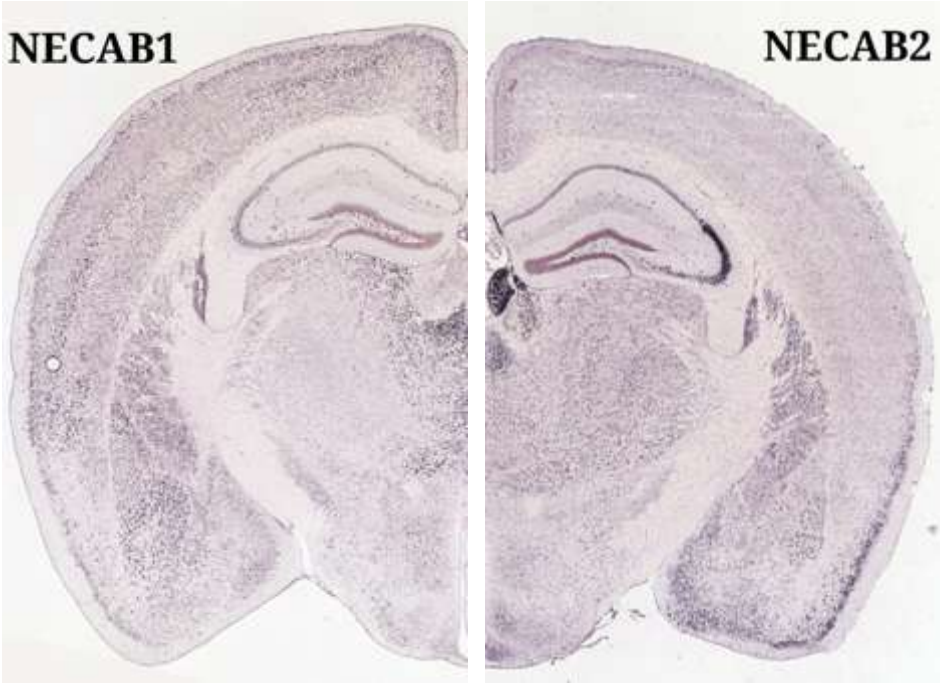
- **Jan Mulder (KI)**
- **Evelina Sjöstedt (KI)**
- **Tomas Hökfelt (KI)**

- Yonglun Luo (BGI, China)
- Csaba Adori (KI)
- Linn Fagerberg (KTH)
- Wen Zhong (KTH)
- Martin Zwahlen (KTH)
- Per Oksvold (KTH)
- Kalle von Feilitzen (KTH)

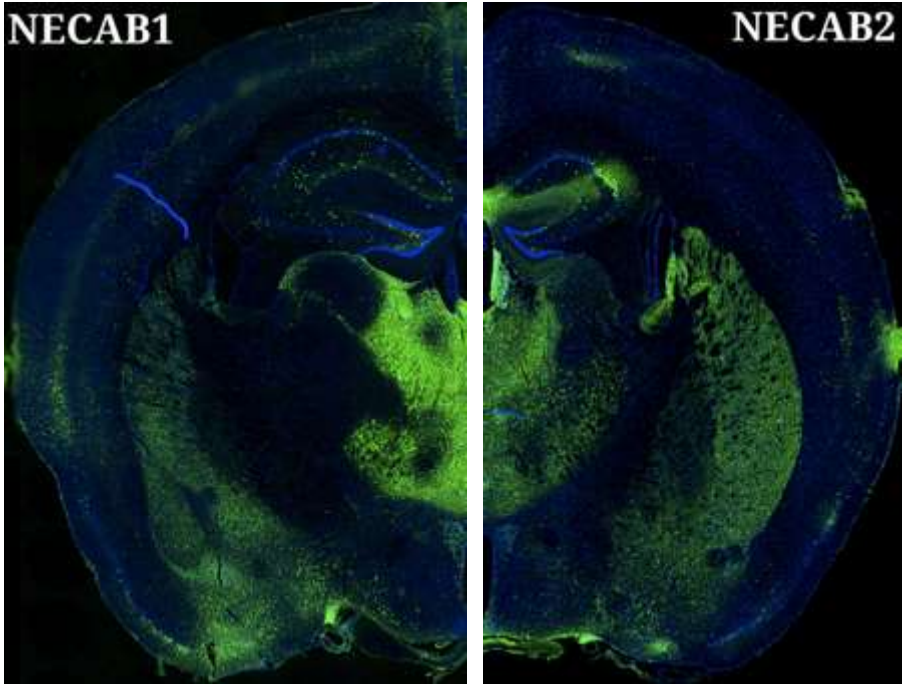
…and many others…

Sjöqvist et al (2019), in review

RNA vs Protein mapping

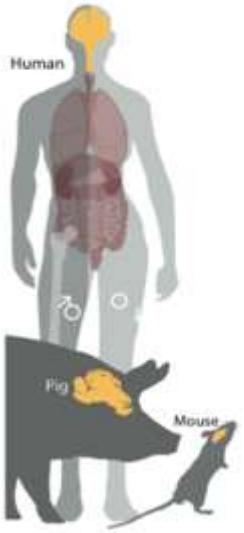


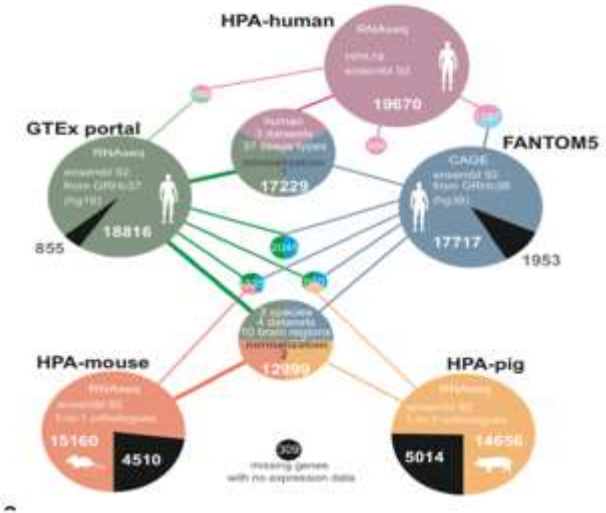
Allen ISH



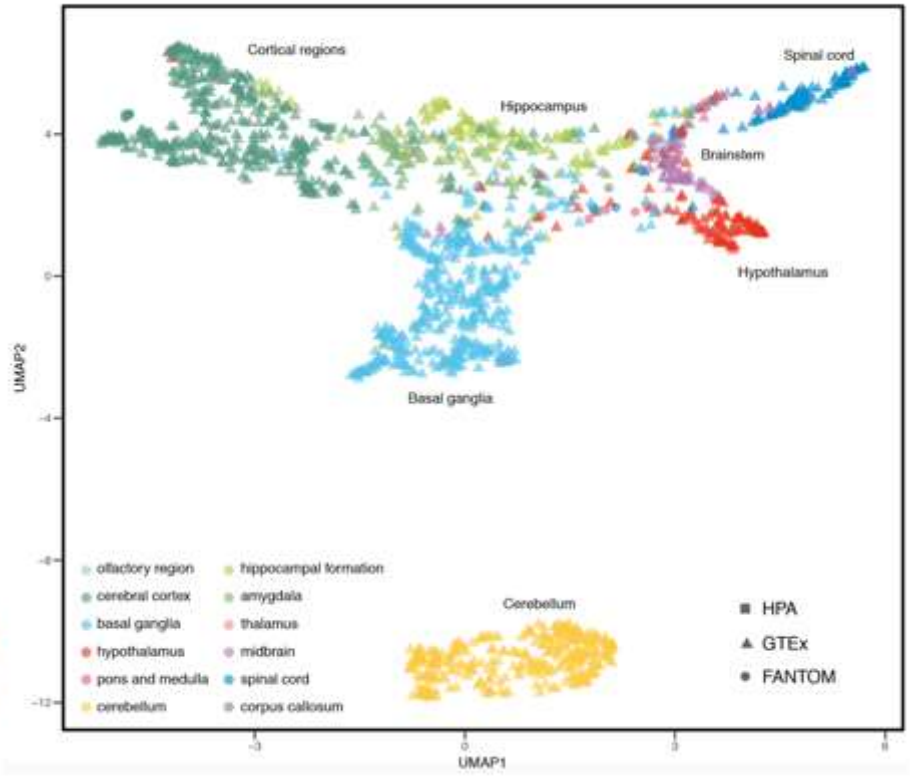
HPA IHC

Normalization of data from several sources and technology platforms



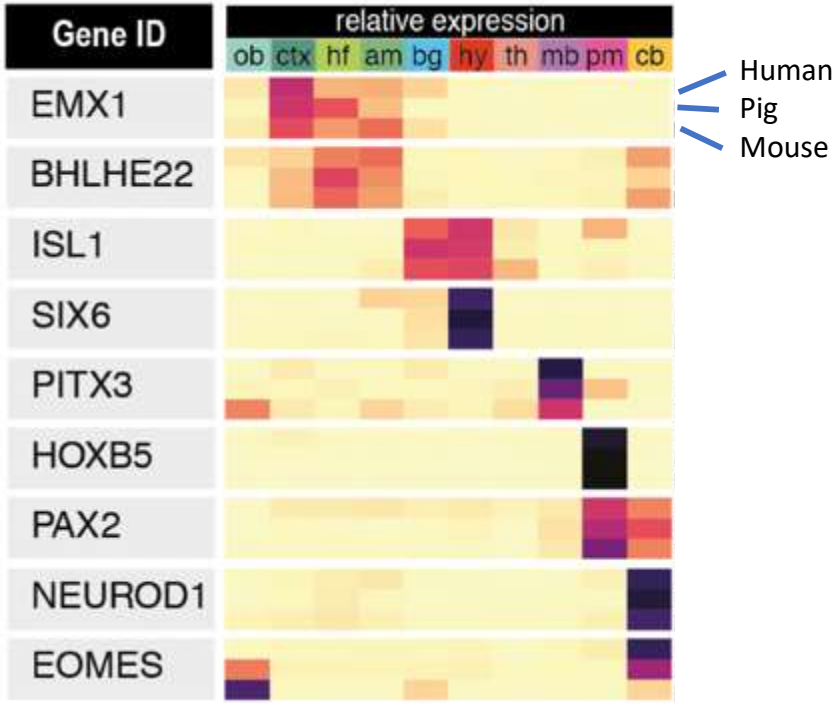


Human brain samples (n=1,047)

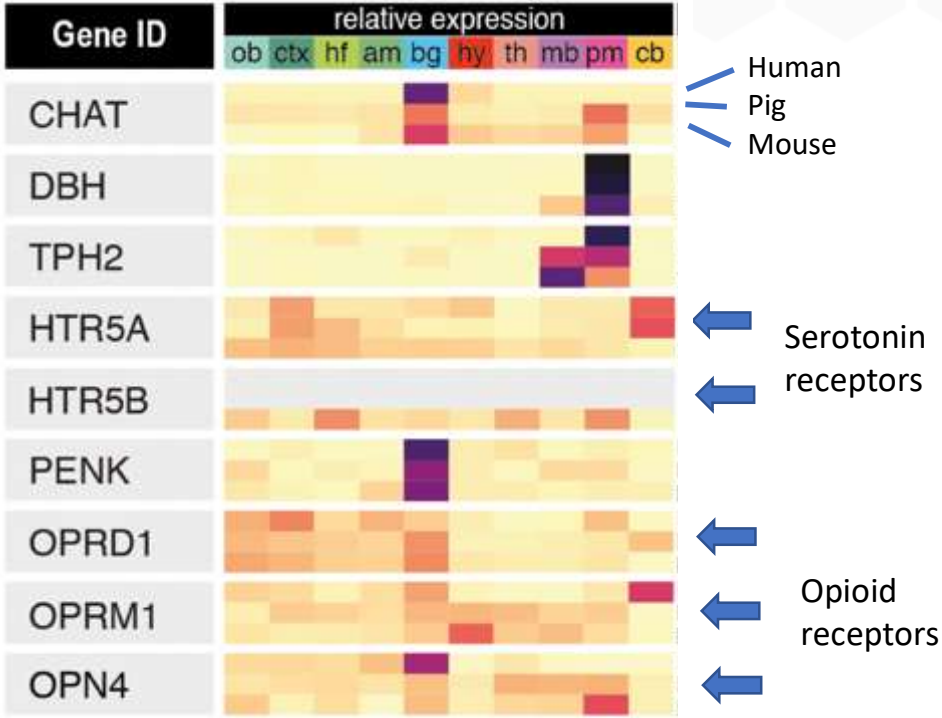


Comparisons of the brains in human, pig and mouse

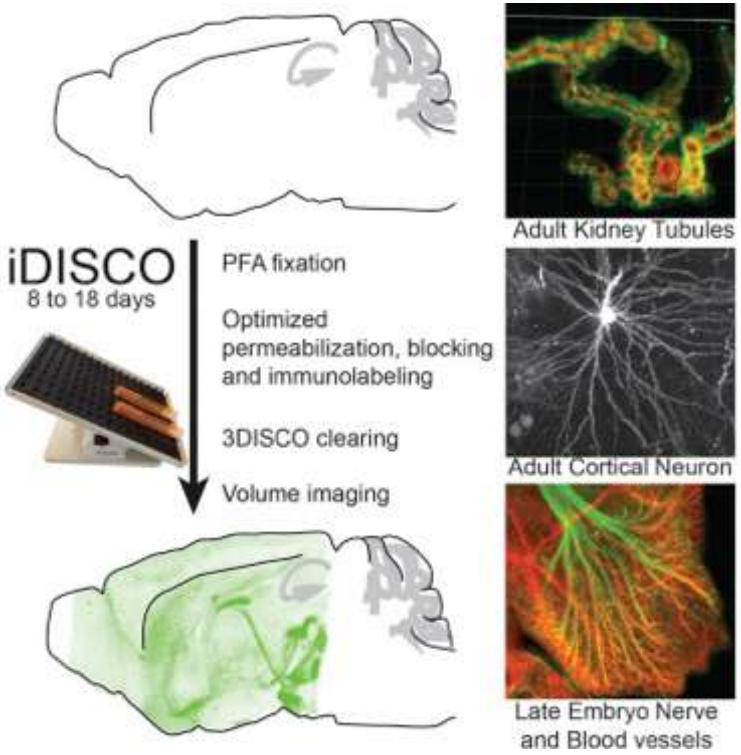
Transcription factors



Neurotransmitters



Single cell 3D-imaging of human brains



Tomas Hökfelt
Csaba Adori
Jan Mulder
Evelina Sjöstedt

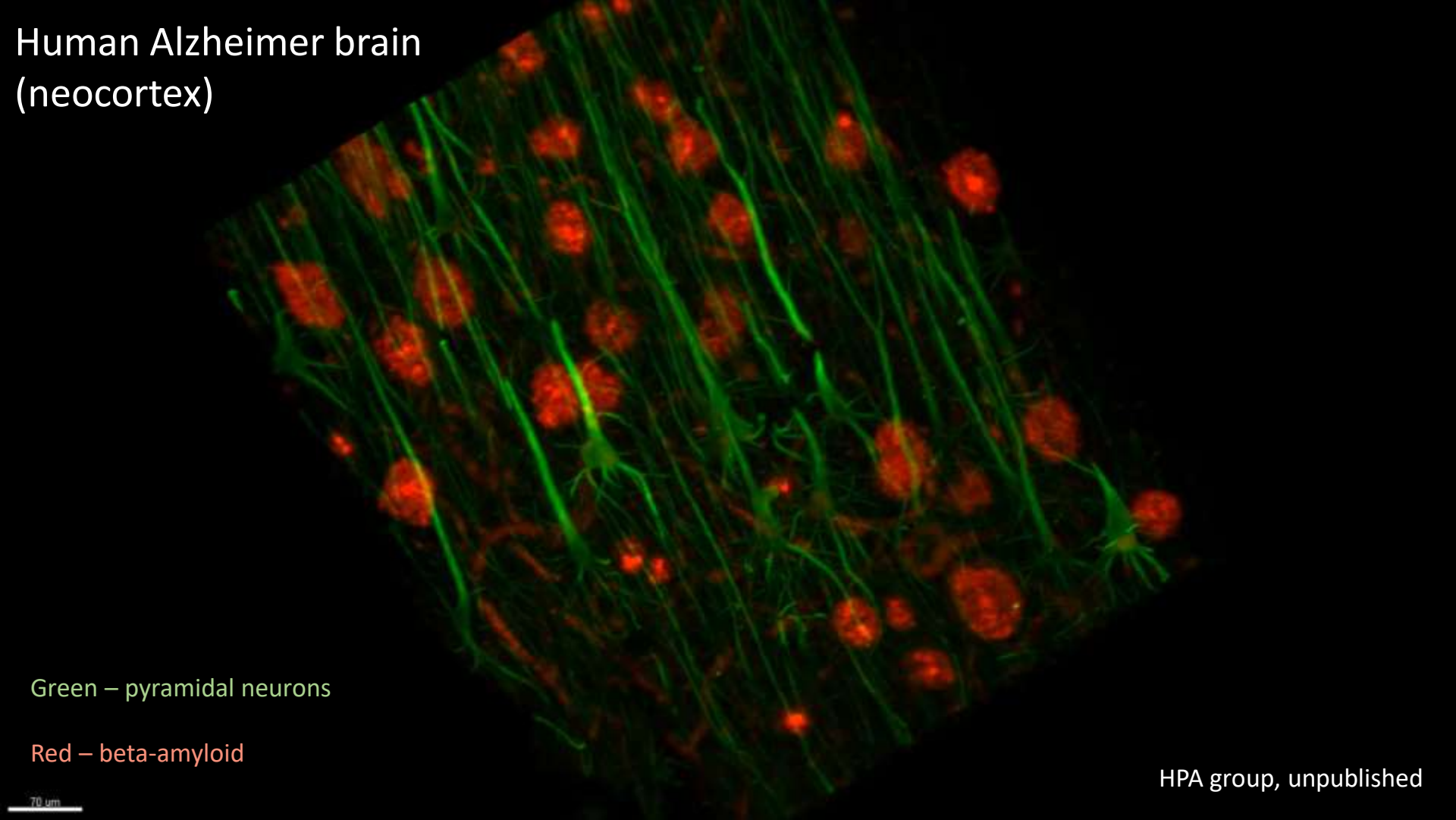
HPA Neuro group
Karolinska Institutet

Tyrosine-hydroxylase in human locus coeruleus

Neurons involved in the
regulation of mood,
sleep and attention

HPA group, unpublished

Human Alzheimer brain (neocortex)

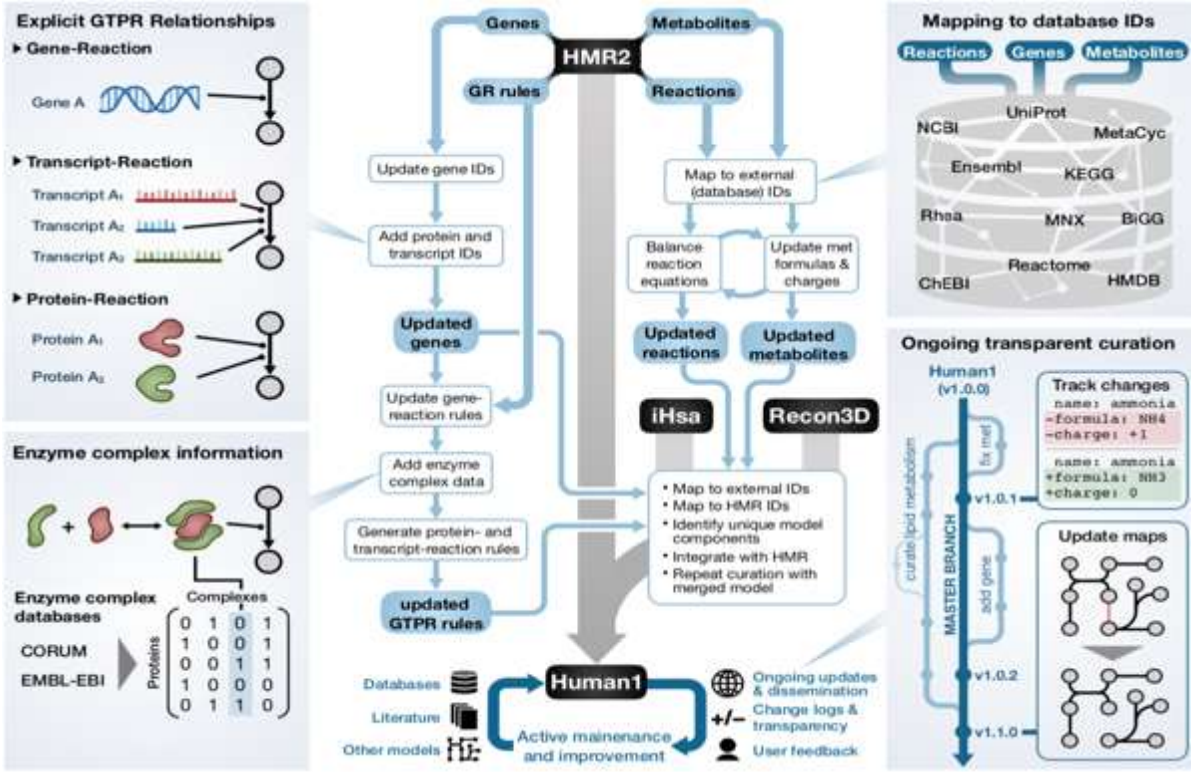


Green – pyramidal neurons

Red – beta-amyloid

HPA group, unpublished

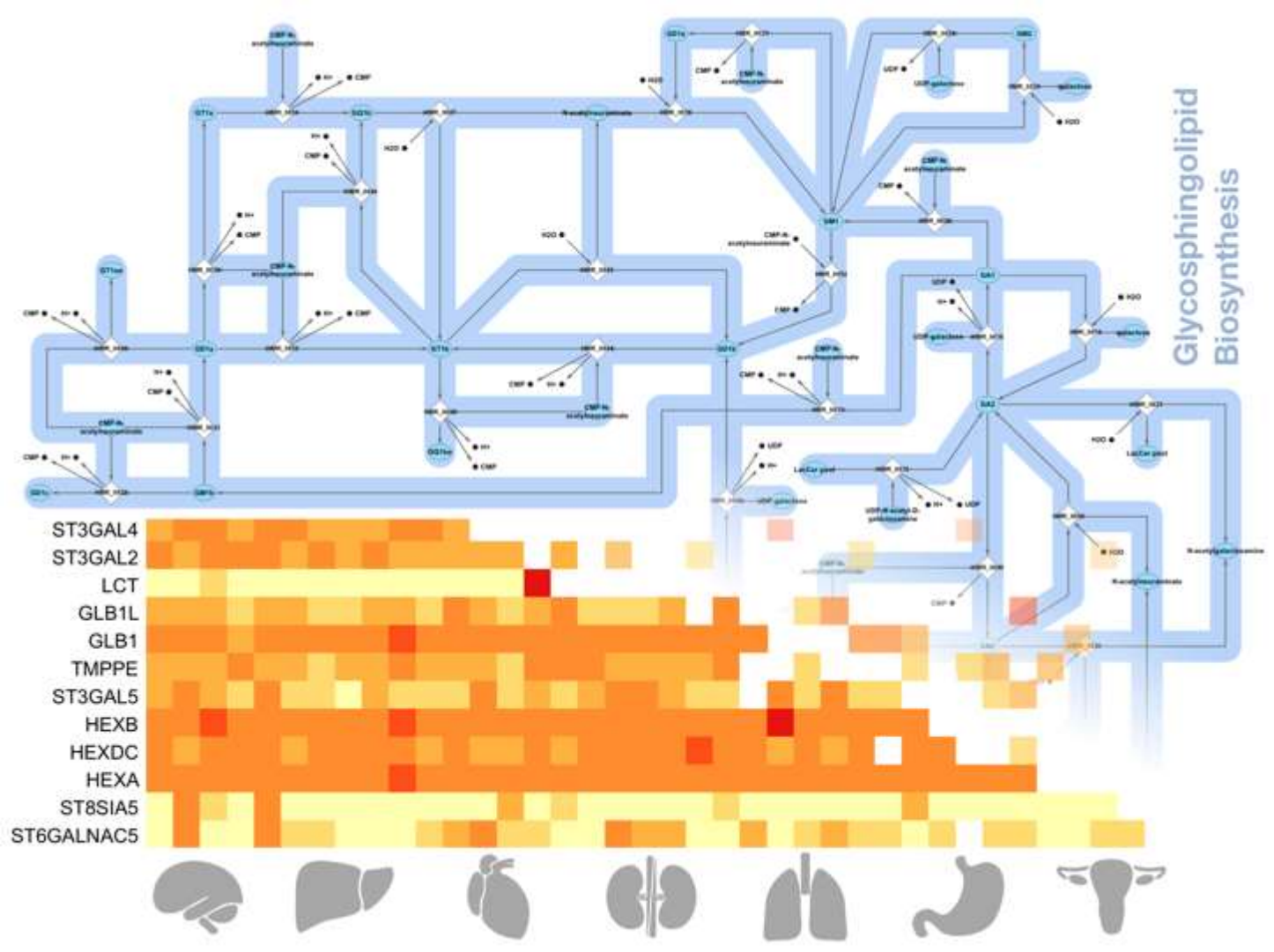
The Metabolic Atlas



6,793 reactions
4,027 metabolites
3,316 genes (enzymes)

Jens Nielsen
Jon Robinson
Mihail Anton

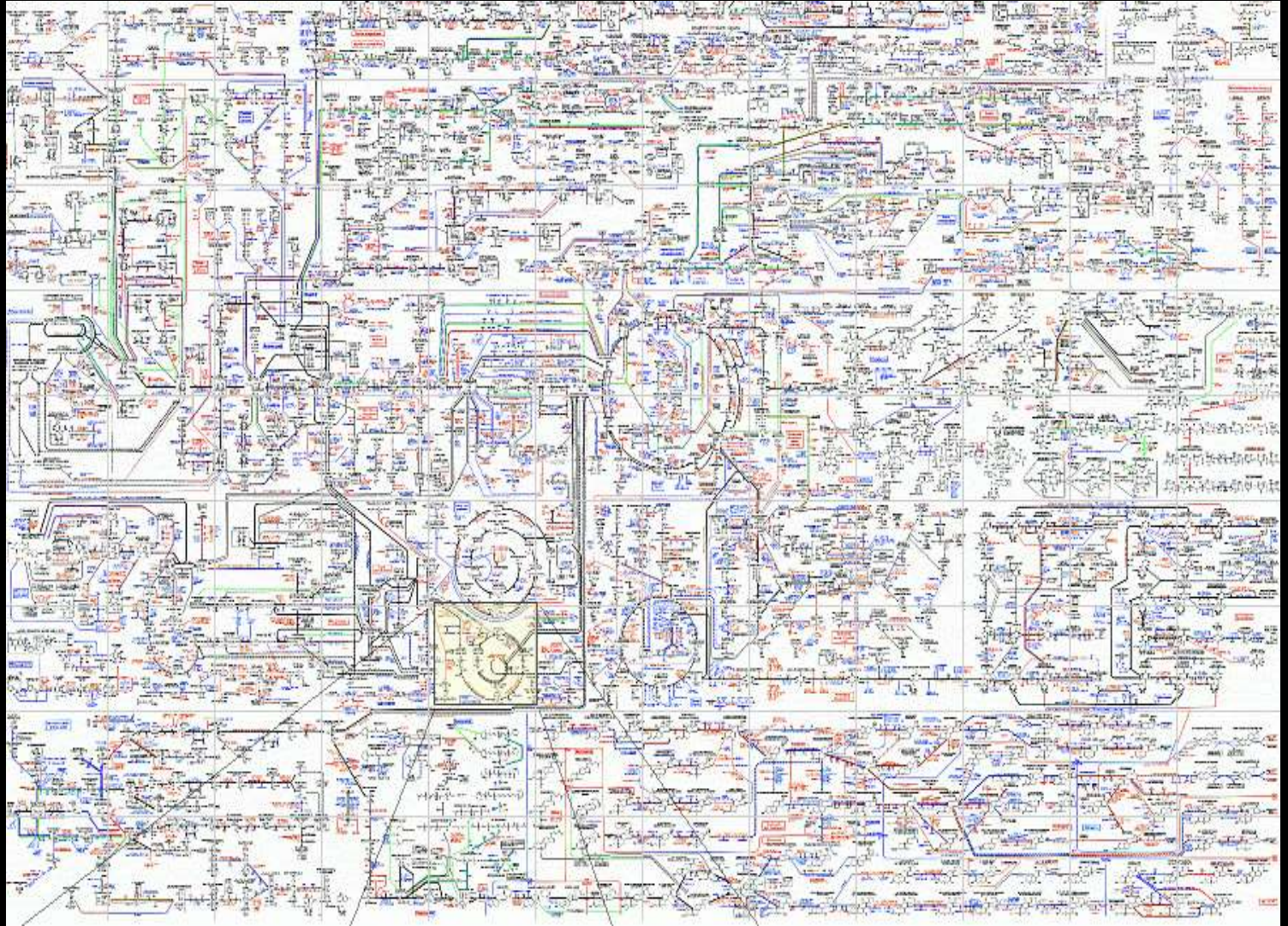
Chalmers
Gothenburg, Sweden



Metabolic Atlas

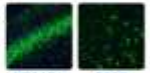
Integrated in the Tissue Atlas

Metabolic Atlas



The Brain Atlas

The Brain Atlas explores the protein expression in the mammalian brain by visualization and integration of data from three mammalian species (human, pig and mouse). Transcriptomic data combined with affinity-based protein in situ localization down to single cell detail is here available in a brain-centric sub atlas of the Human Protein Atlas. The data focuses on human genes and one to one orthologues in pig and mouse. Each gene is provided with a summary page, showing available expression data (mRNA) for summarized regions of the brain as well as protein location for selected targets. High resolution staining images as well as expression data for the individual sub regions are all available for exploring the most complex organ.



THE BRAIN

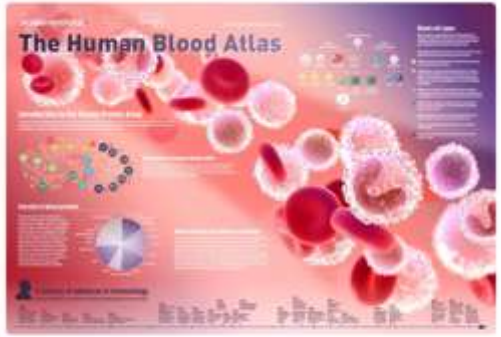
Gene classification based on expression in tissue types representing the whole human body enables the description of brain elevated proteins. Regional expression data is used for further brain - in depth classification, highlighting the complexity of the brain. Regional classification is performed in human, pig and mouse brain separately by comparing transcriptomic data summarized into 10 main regions of the brain. The regional classification in human brain is also compared to whole-body expression. The combination of transcriptomic data and antibody-based protein profiling is investigated on separate summary pages as a platform for further exploring the brain proteome.

BRAIN REGIONS

Explore the various regions of the brain

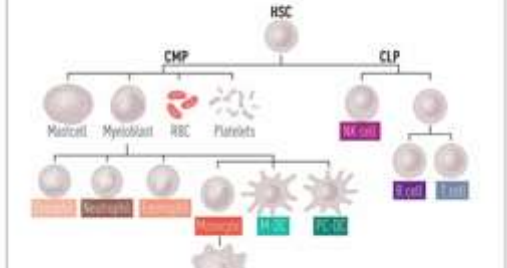
Brain samples are grouped into 10 anatomical regions, providing regional classification of >16,000 genes based on RNA expression, indicating which proteins are elevated in one region compared to the other.

The Blood Atlas



The Blood Atlas contains single cell type information of genome-wide RNA expression profiles of human protein-coding genes covering various B- and T-cells, monocytes, granulocytes and dendritic cells. The single cell transcriptomics analysis covers 18 cell types isolated with cell sorting followed by RNA-seq analysis. In addition, an analysis of the "human secretome" is presented including annotation of the genes predicted to be actively secreted to human blood, as well as the annotation of proteins predicted to be secreted to other parts of the human body, such as the gastric tract and local compartments. An analysis of the proteins detected in human blood are also presented with an estimation of the respective protein concentrations determined either with mass spectrometry-based proteomics or antibody-based immune assays.

THE HUMAN BLOOD CELLS



The Metabolic Atlas

The Metabolic Atlas portion of the Tissue Atlas enables exploration of protein function and tissue-specific gene expression in the context of the human metabolic network. For proteins involved in metabolism, a metabolic summary is provided that describes the metabolic subsystems/pathways, cellular compartments, and number of reactions associated with the protein. Over 120 manually curated metabolic pathway maps facilitate the visualization of each protein's participation in different metabolic processes. Each pathway map is accompanied by a heatmap detailing the mRNA levels across 37 different tissue types for all proteins involved in the metabolic pathway.

METABOLIC MAPS

Maps are organized by individual pathways to facilitate visualization of metabolic areas of interest. Further detail and full cellular compartment maps are available at metabolicatlas.org.

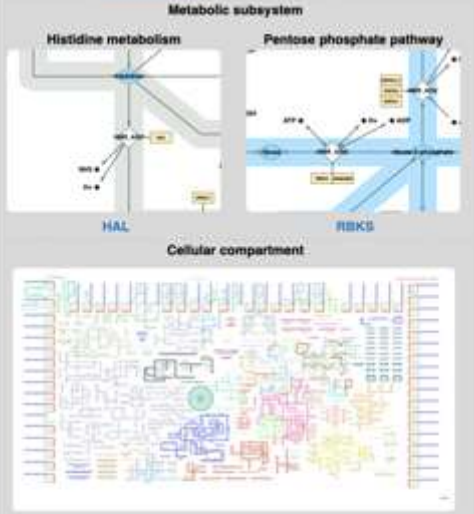


Table 1. A complete list of the pathways details in the Metabolic Atlas and number of enzymes involved in each pathway.

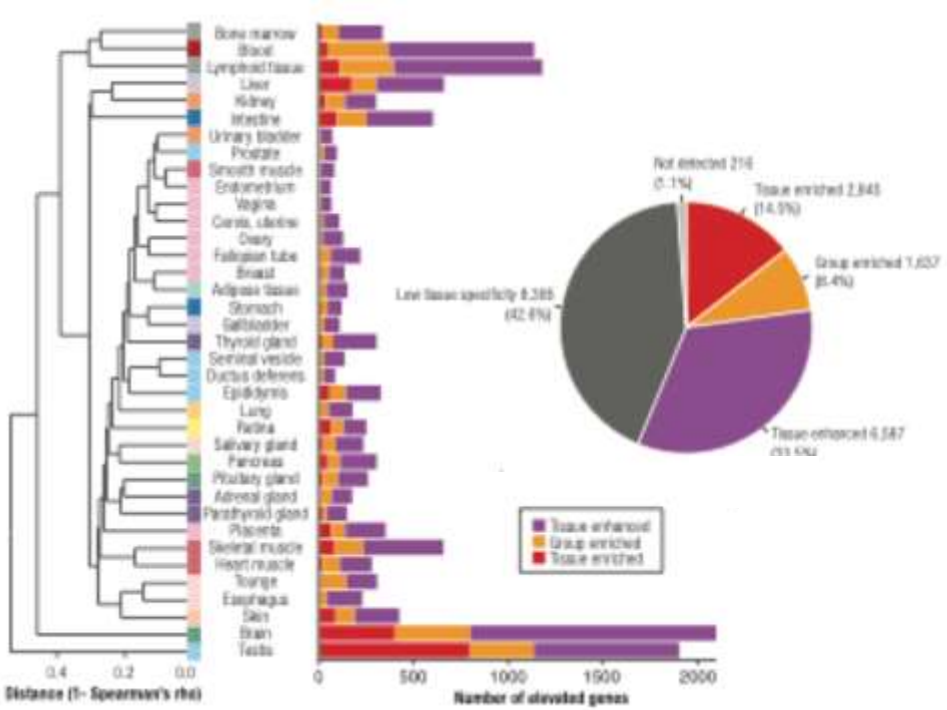
Pathway	# genes
Acyl-CoA hydrolysis	8
Acylglycerides metabolism	38

2.

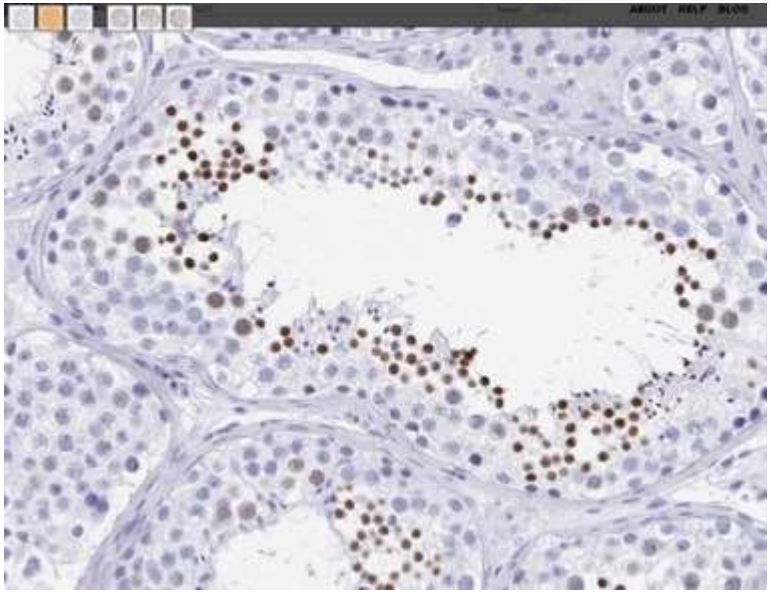
The Human Proteome –

an update

New classification of all human genes (tissue specificity)



Hepataoma derived growth-like factor 1 (testis)

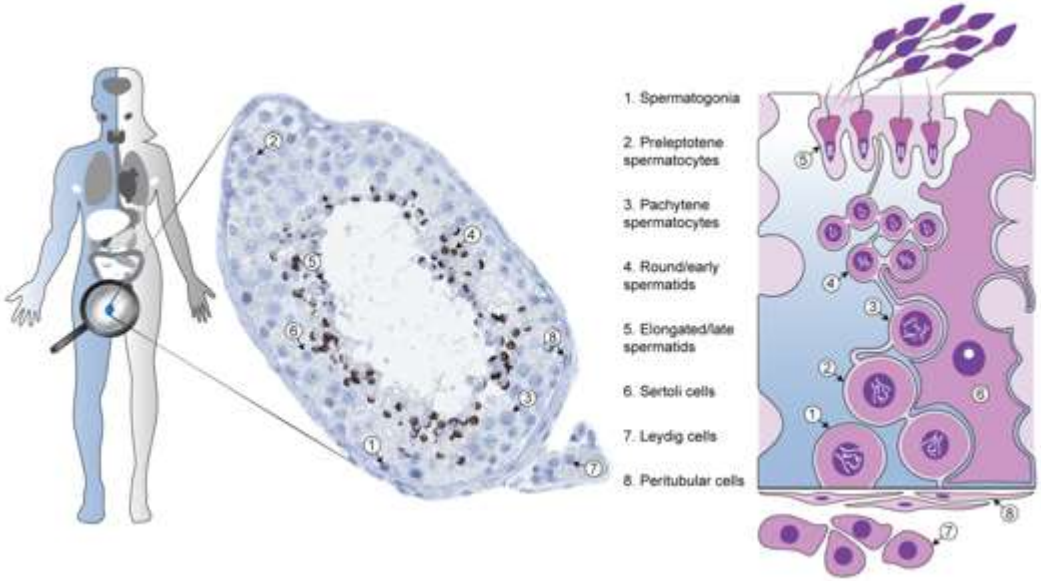


4,482 genes (23%) are enriched in human tissues or organs

Only 586 genes (3%) are ”specific” for one tissue (including insulin, troponin and PSA)

Uhlen et al, in review

Deep annotation of testis-specific proteins



- In-depth characterization of 500 testis elevated genes
- Detailed analysis of spatial protein localization in 8 testicular cell types

Journal of proteome research

Article

pubs.acs.org/jpr

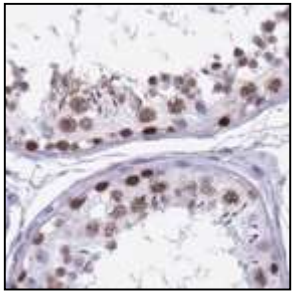
Cell Type-Specific Expression of Testis Elevated Genes Based on Transcriptomics and Antibody-Based Proteomics

Charles Pineau,[†,‡] Feria Hikmet,[†] Cheng Zhang,[†] Per Oksvold,[†] Shuqi Chen,[†] Linn Fagerberg,[†] Mathias Uhlén,[†] and Cecilia Lindskog*[,†]

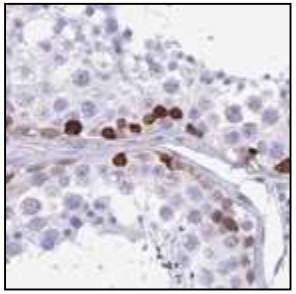
Dr. Cecilia Lindskog
Head Tissue Atlas
Human Protein Atlas

Dr. Charles Pineau
Inserm, France

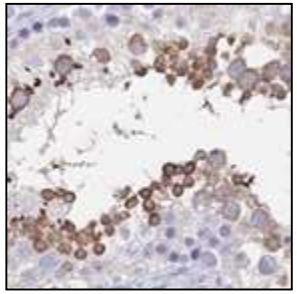
Cells in seminiferous ducts (testis)



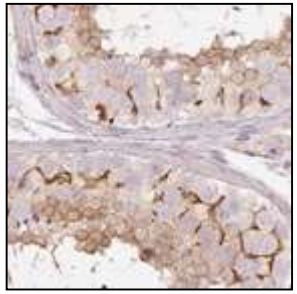
VCY1B
All germ cells



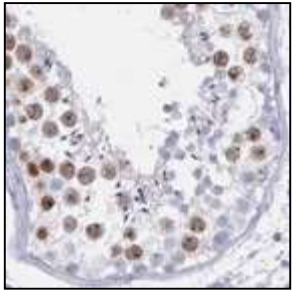
TSPY1
Spermatogonia and preleptotene spermatocytes



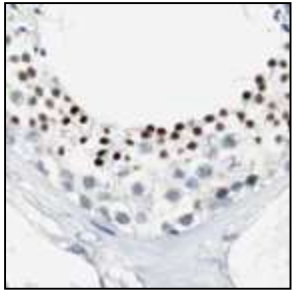
SHCBP1L
Pachytene spermatocytes, round/early spermatids and elongated/late spermatids



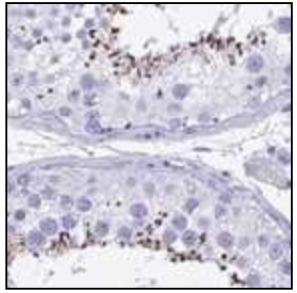
SLCO6A1
Sertoli cells, round/early spermatids and elongated/late spermatids



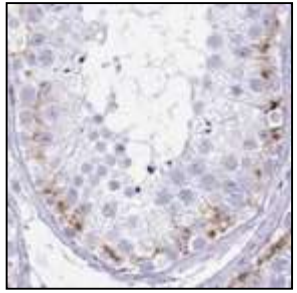
SYCP3
Pachytene spermatocytes



SOX30
Round/early spermatids

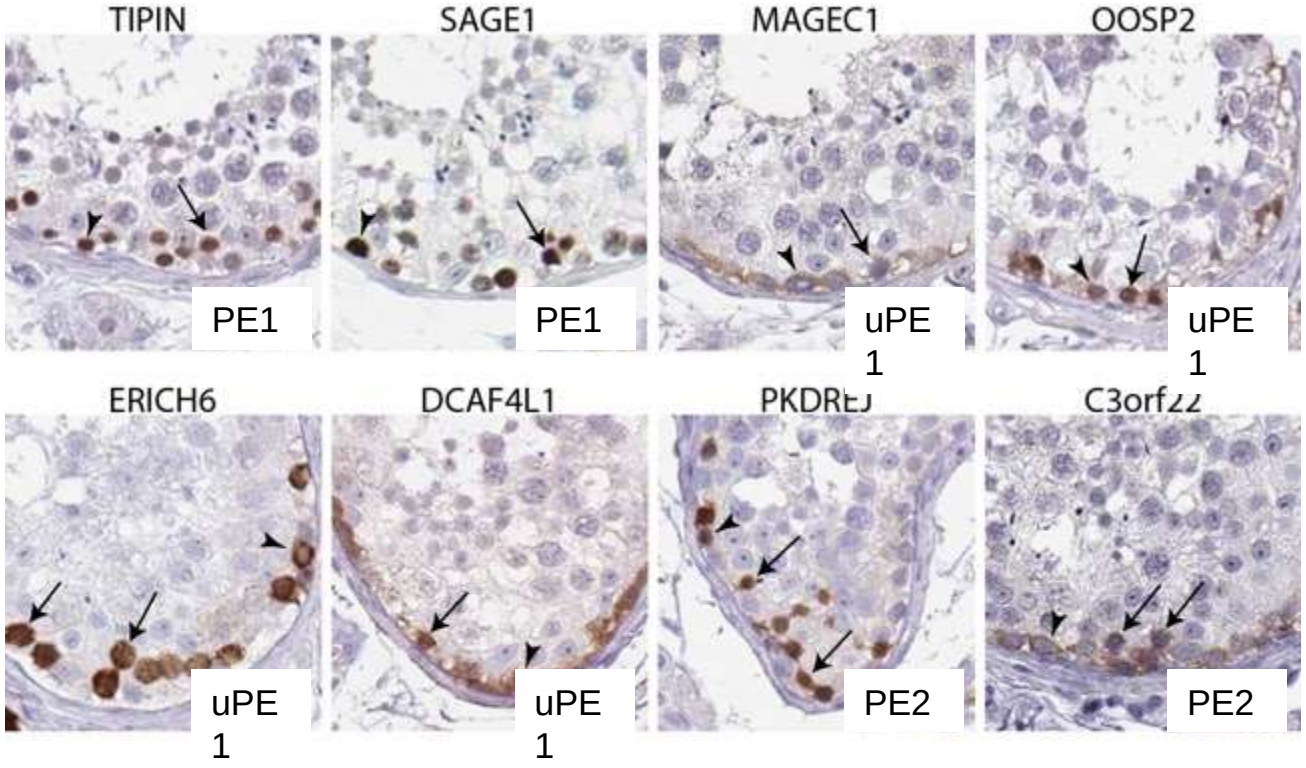


BPIFA3
Elongated/late spermatids



TEX19
Sertoli cells

Protein expression in premeiotic cells

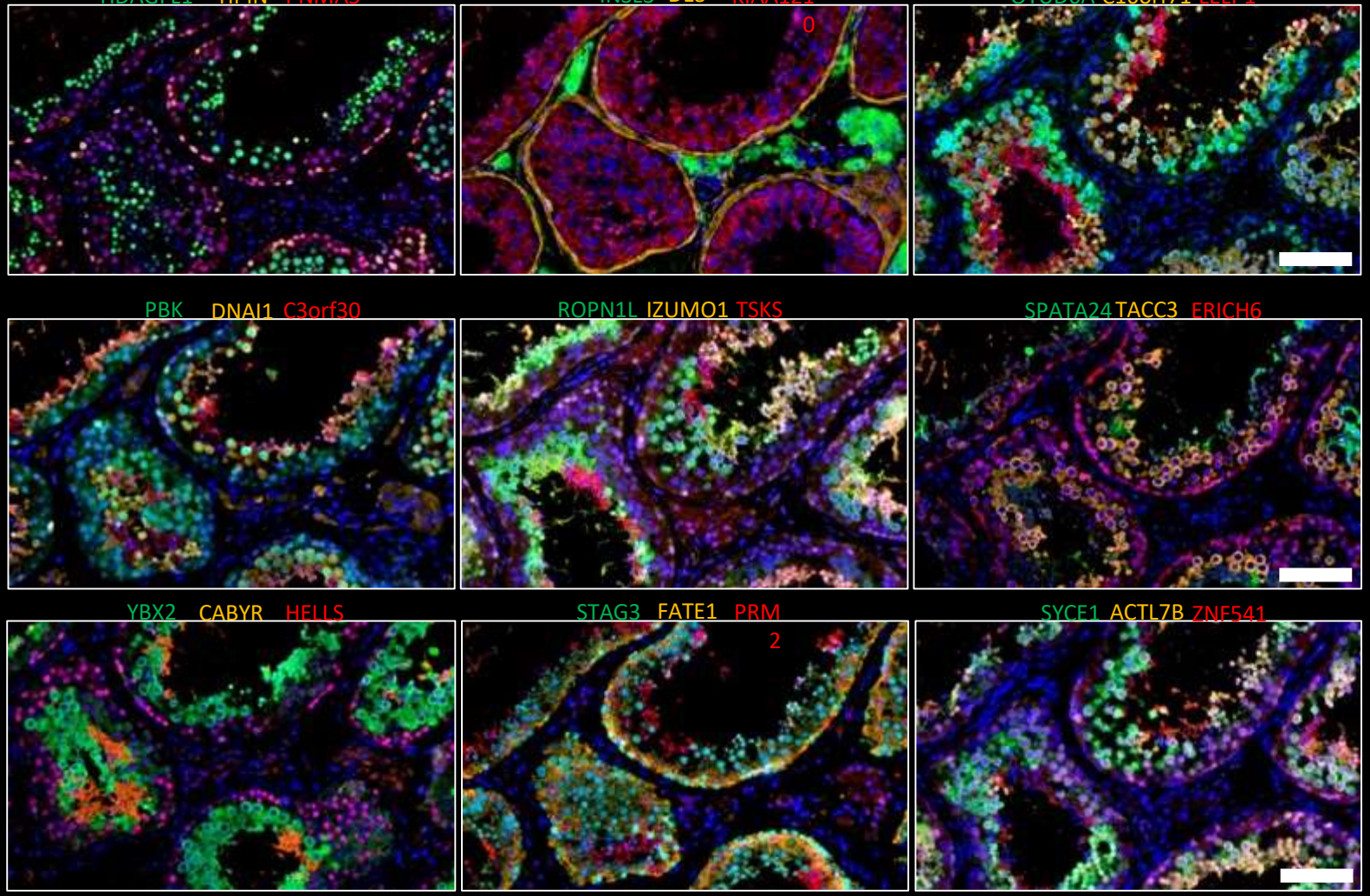


57 proteins

11 proteins with unknown function

10 ”missing proteins”

Involved in cell division and differentiation



Testis

Multiplex staining

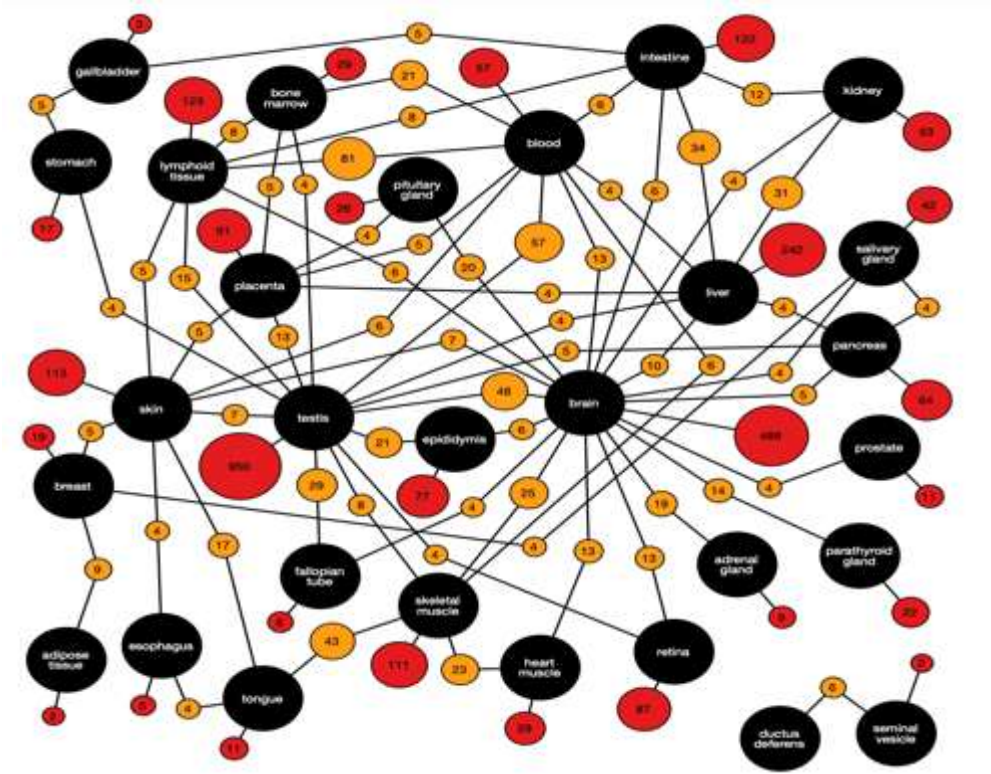
Evelina Sjöstedt

Feria Hikmet

Dennis Kesti

Cecilia Lindskog

Map of the tissue enriched genes



n=4,482

THE HUMAN PROTEIN ATLAS

Uhlen et al, in review

How many proteins in humans ?

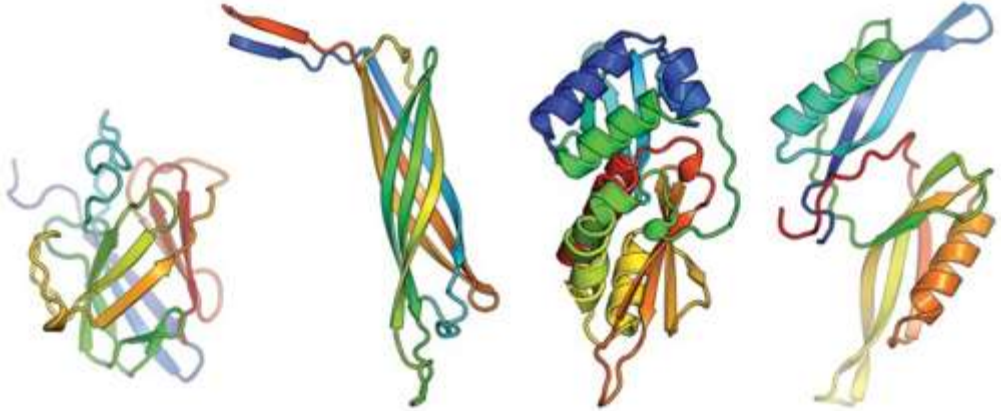
Type	Number	Comment
Protein-coding genes	19,670	The protein existence confirmed for 17,723 genes (90%)
Splice variants (isoforms)	82,271	So far, few examples of new functionalities (but interesting to explore)
Protein modifications	>200,000	Modulate activity in enzymes and signal pathways
Somatic re-arrangements	>20,000,000	The creation of immunological memory (IgG and T-cell receptors)

Status September 2019

Evidence for protein-coding genes

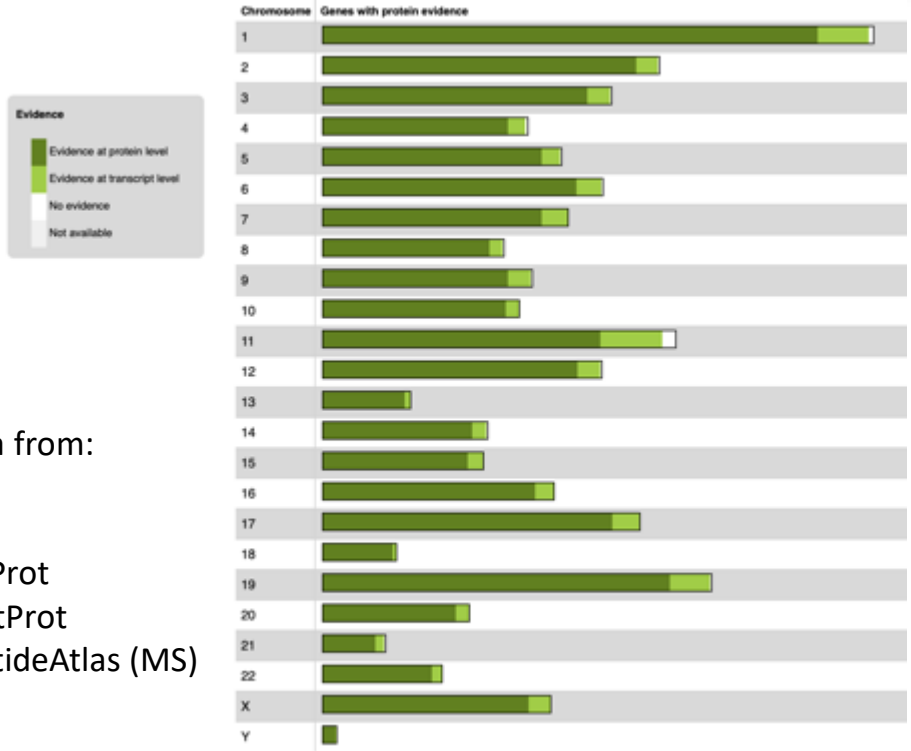
Altogether 19,670 predicted protein-coding genes (September 2019)

- 17,723 with evidence on the protein level (mainly antibody-based)
- 1,833 with evidence on transcriptional level
- 114 with no evidence (keratins, olfactory receptors and AC genes)



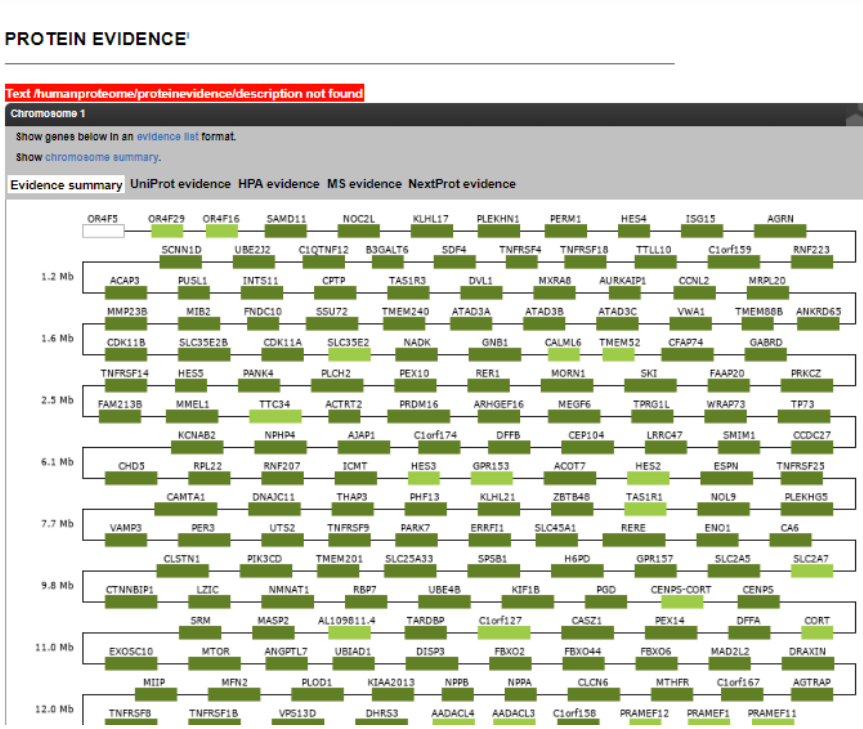
THE HUMAN PROTEIN ATLAS

Evidence for protein existence – chromosome summary



Data from:

HPA
UniProt
NextProt
PeptideAtlas (MS)



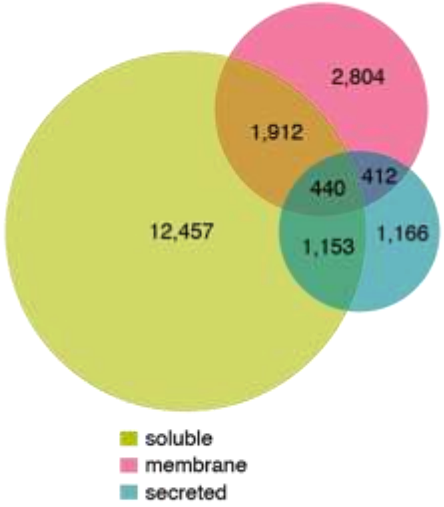
www.proteinatlas.org

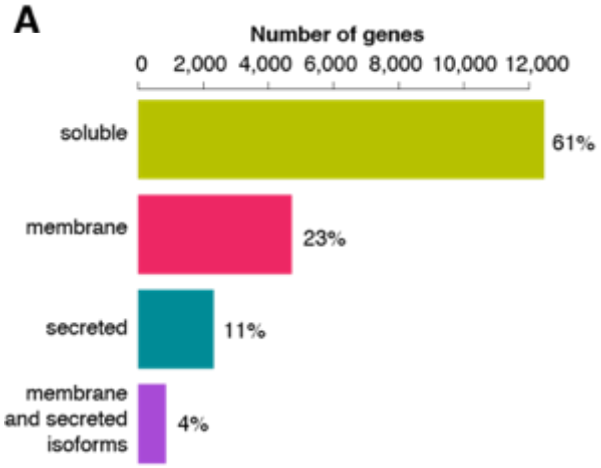
Chromosome 1

3.

The human secretome project

THE SECRETOME AND MEMBRANE PROTEOME





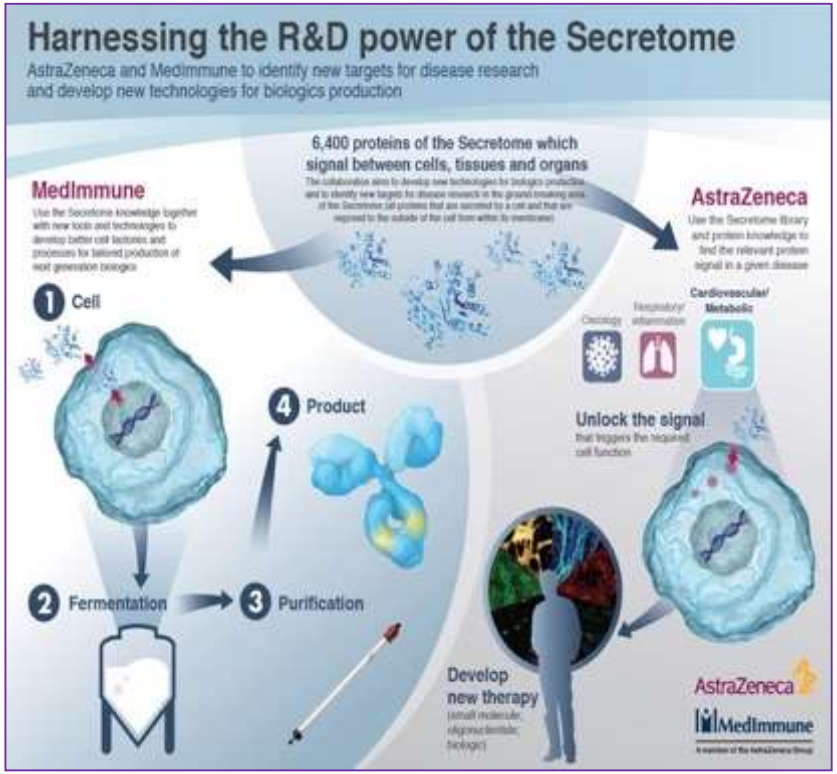
- 3000 secreted proteins
- 5500 membrane-bound proteins

Uhlen et al Science, 2015

The Human Secretome Project (HSP)

Overall objective:

- Production of all human secreted proteins
- High-throughput production in CHO cells
- Create a resource of reagents for drug discovery and development



Human Secretome Project

- 3017 genes have been generated with synthetic biology
- 1600 bioactive proteins have been produced in CHO cells .
- Phenotypic assay have been run in collaboration with AstraZeneca

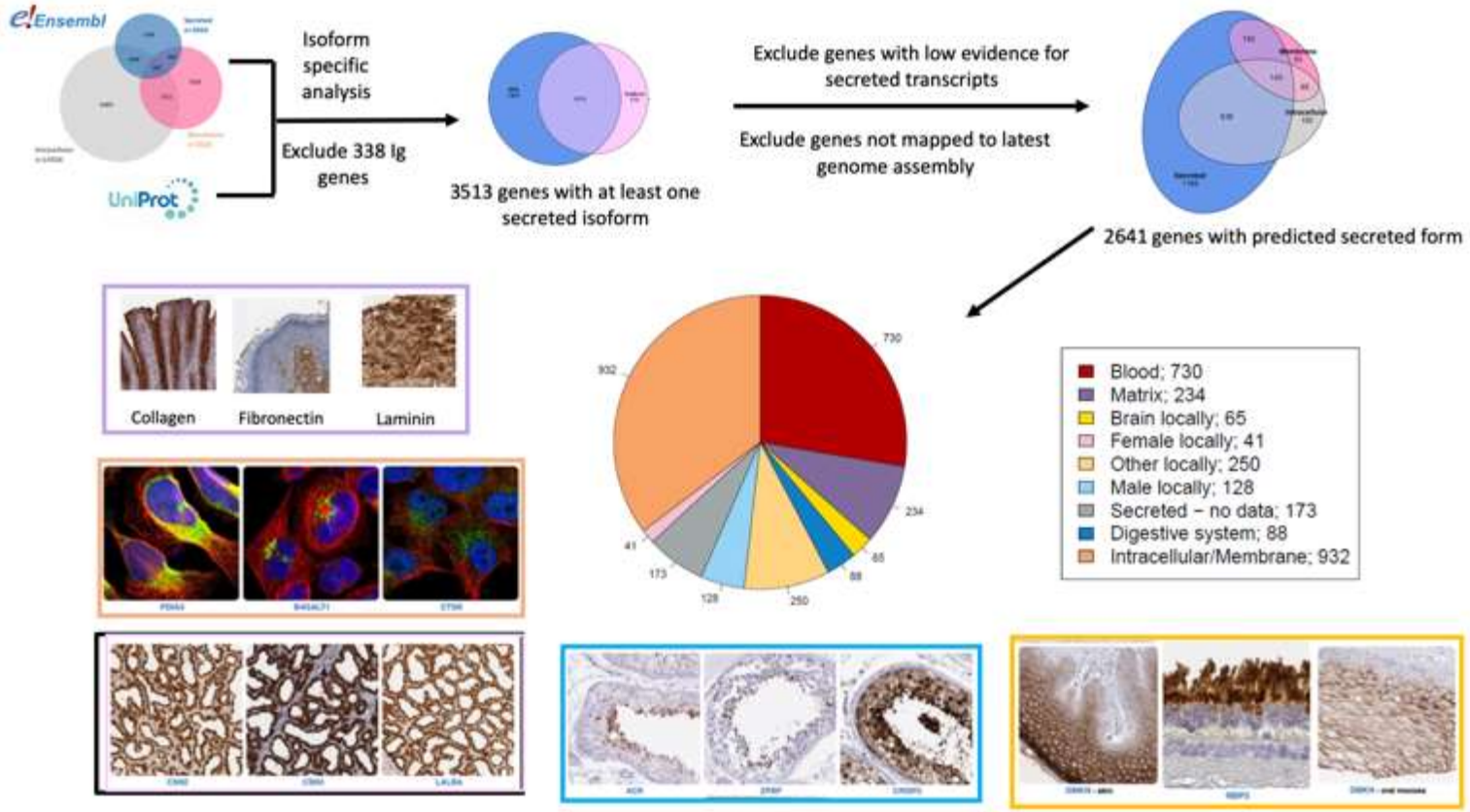
KTH

Knut och Alice Wallenbergs Stiftelse

novo nordisk fonden

AstraZeneca
IMED Biotech Unit

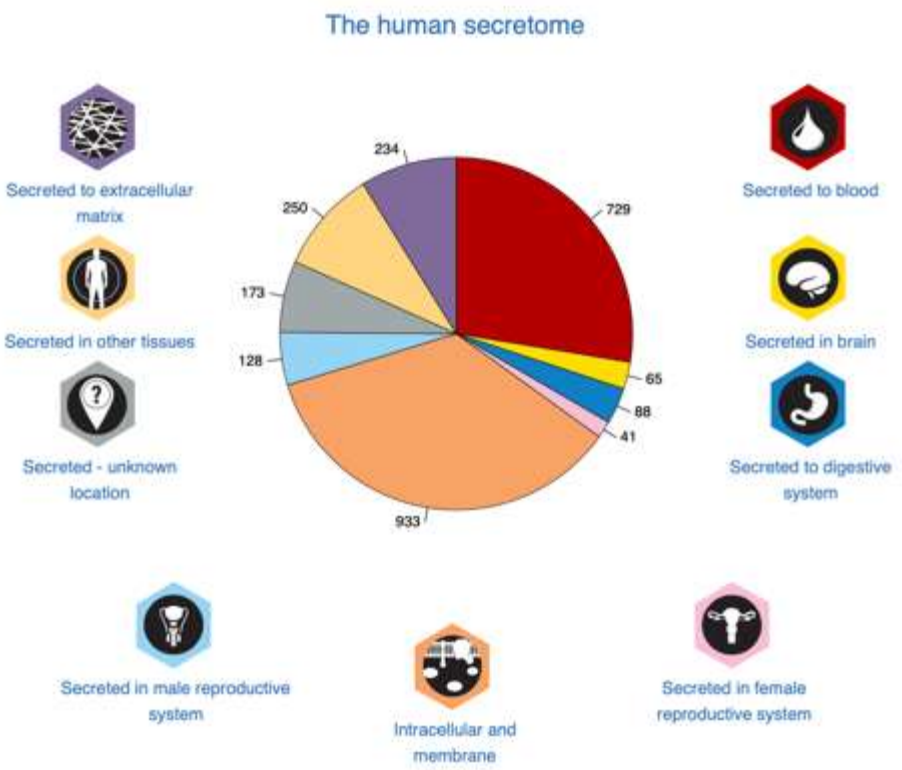
How many secretome proteins in humans ?



Åsa Sivertsson

Uhlen et al, submitted

The human secretome



All input from community welcome

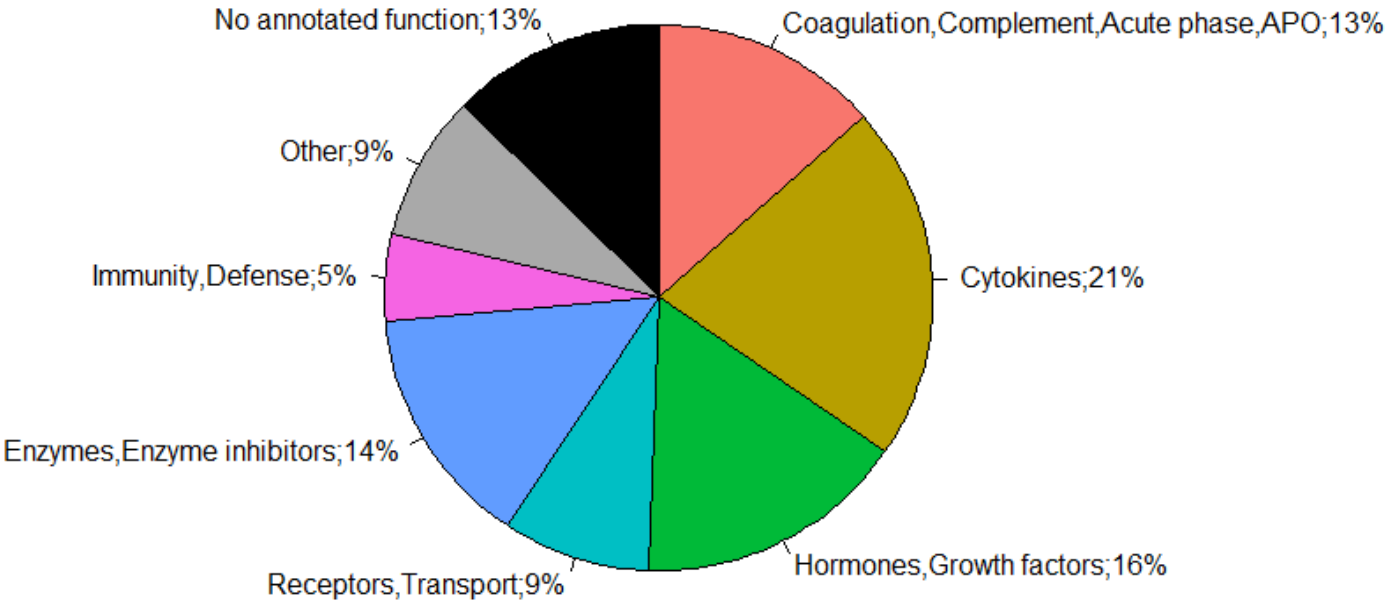
Human secretome contributors:

- **Åsa Sivertsson (KTH)**
- Sophia Hober (KTH)
- Hanna Tegel (KTH)
- Fredrik Edfors (KTH)
- Andreas Hober (KTH)
- Jochen Schwenk (KTH)
- Adil Mardinoglu (KTH)
- Wen Zhong (KTH)
- Cheng Zhang (KTH)
- Peter Nilsson (KTH)
- Linn Fagerberg (KTH)
- Martin Zwahlen (KTH)
- Per Oksvold (KTH)
- Kalle von Feilitzen (KTH)

…and many others…

Uhlen et al (2019B), in review

Function of the human blood secretome (n=729)

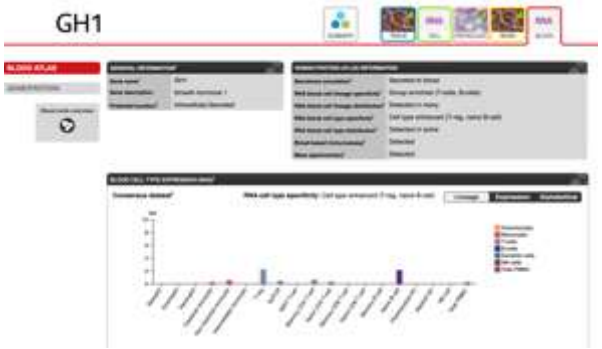


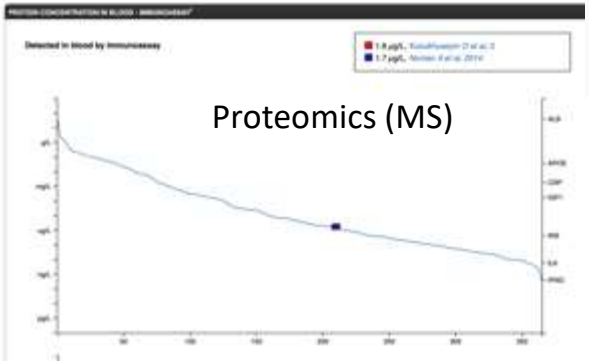
Human plasma proteins (part of the Blood Atlas)

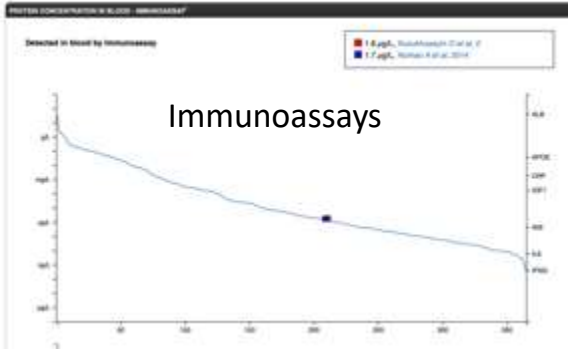
The estimated protein concentrations of proteins detected in human plasma based on:

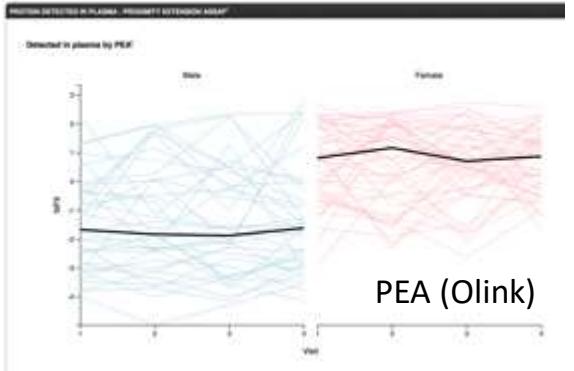
1. AB-based immunoassays
2. Mass spectrometry-based proteomics
3. Ab-based Proximity Extension Assay

Human Growth Horomone



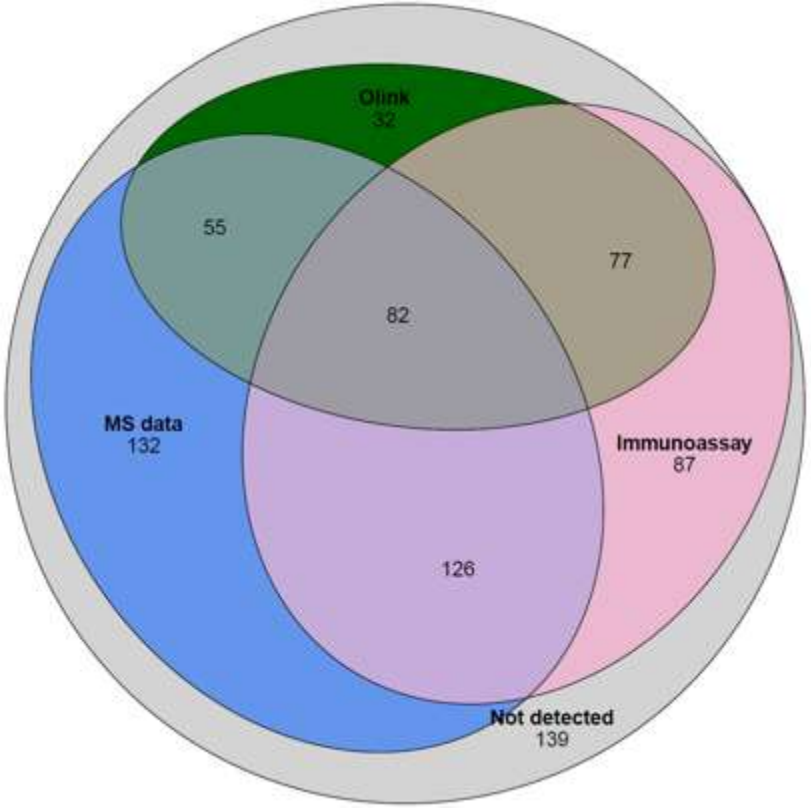






Objective: make assays to the whole blood proteome

- Proteomics (PeptideAtlas)
- Immunoassays (literature)
- Olink assays (“in-house”)
- Not detected



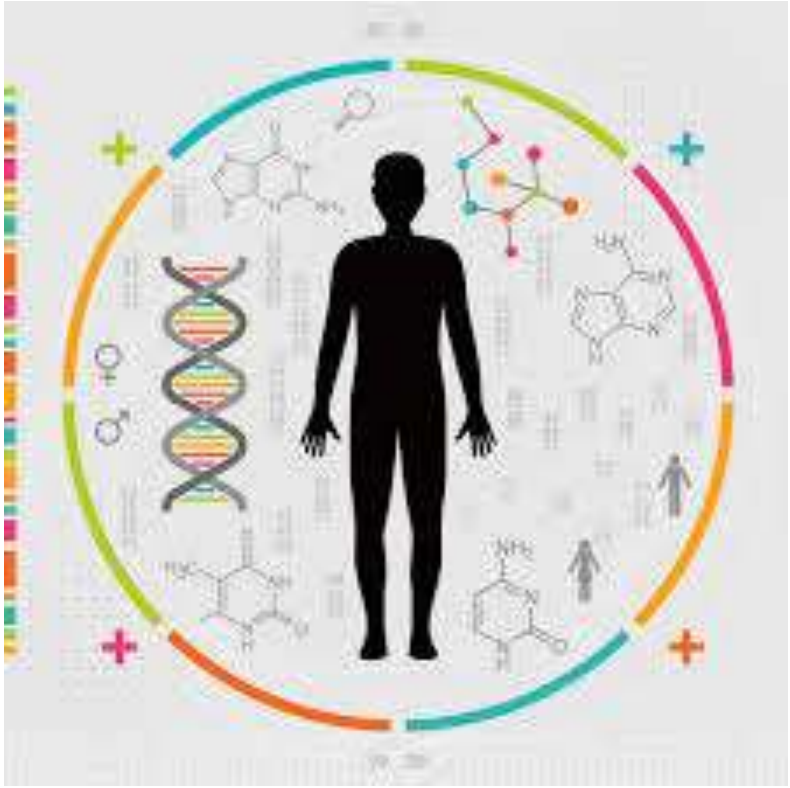
Total: 729 blood proteins

139 not detected by any of the three platforms

4.

Precision medicine – an introduction

Precision medicine



Right treatment to right patient

More targeted treatment with less side-effects (biologicals)

Better diagnostic methods for analysis of health and disease

Diagnostic tools in hospitals and primary care

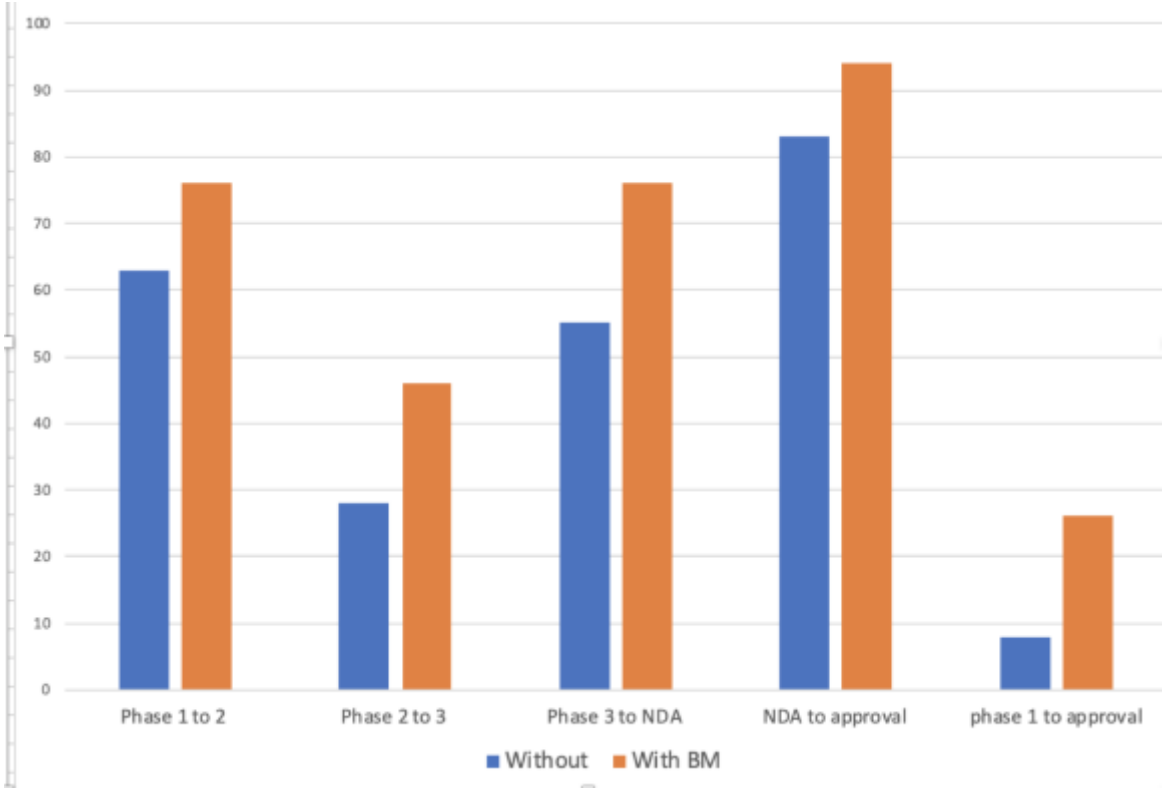
Classical analysis

- Blood sedimentation rate
- Blood pressure
- Puls
- EKG
- Oxygen levels (in blood)
- Spirometry
- Colonoscopy
- Ultrasound
- X-ray
- CRP (inflammation)
- Urine stick
- DNA-tests
- Troponin

New analysis

- Streptokock (quick tests)
- Sexual diseases (home kits)
- DNA-sequencing (nisch applications)
- Glucose – real time measurements (diabetes)
- Helicobacter (breath)
- Medical imaging

Probability of success in clinical phase transitions (n=9,985) with biomarkers involved in patient stratification



Source: Taiho pharma (unpublished)

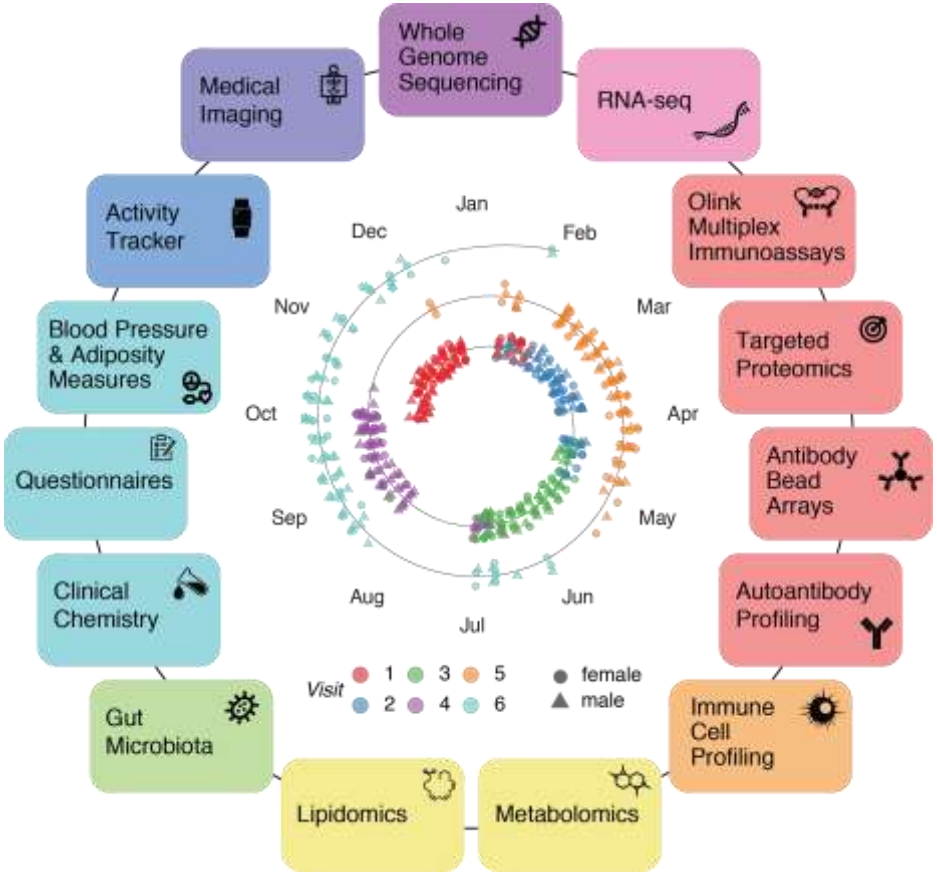
Proteomics profiling of blood proteins

- Criteria:
  - More than 1000 targets
  - Precision - low technical variance (CV)
  - Specificity (low off target binding)
  - Multiplex (parallel) assays
  - Sensitivity (cytokine levels)

- Two competing platforms:
  - Olink (Uppsala, Sweden)
  - Somalogic (Boulder, Colorado, US)

- Not (yet) competitive:
  - Sandwich assays (ELISA etc)
  - Luminex
  - Proteomics (MS-based)

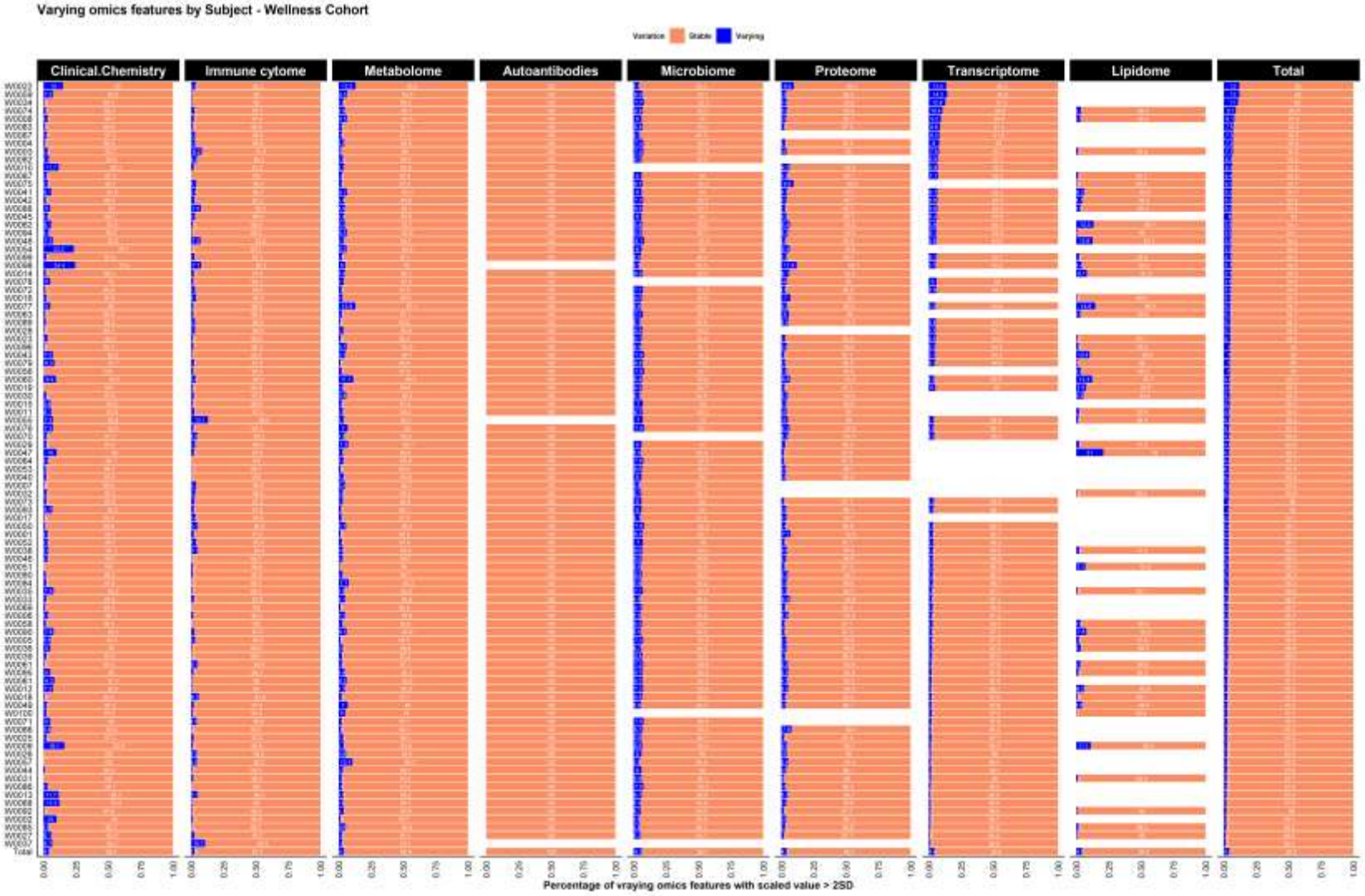
The Swedish SCAPIS SciLifeLab Wellness Profiling (S3WP) program



Vision

To define the "wellness profile" of individuals using state-of-the art molecular analyses

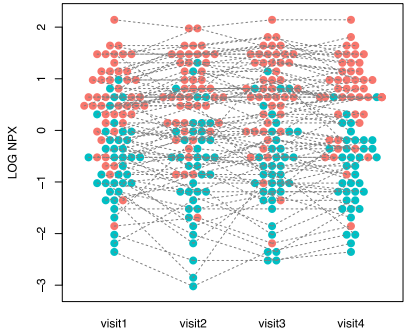
- Combine "classical" diagnostics, advanced imaging and new omics technologies
- Detect early signs of diseases
- Guide individualized treatments


Varying omics features by Subject - Wellness Cohort
Variance
Stable
Varying
Clinical.Chemistry
Immune cytome
Metabolome
Autoantibodies
Microbiome
Proteome
Transcriptome
Lipidome
Total
0.00
0.25
0.50
0.75
1.00
Percentage of vraying omics features with scaled value > 2SD

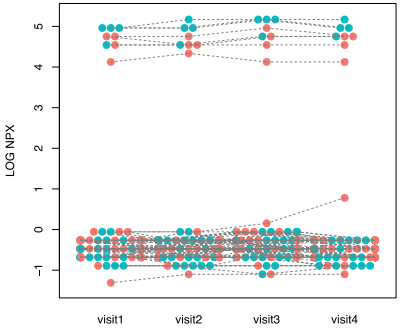
Plasma protein profiling

- Olink multiplex panels based on proximity extention assay (PEA)
- 397 samples run in 11 panels with 92 proteins in each
- Longitudinal data for ~1000 proteins

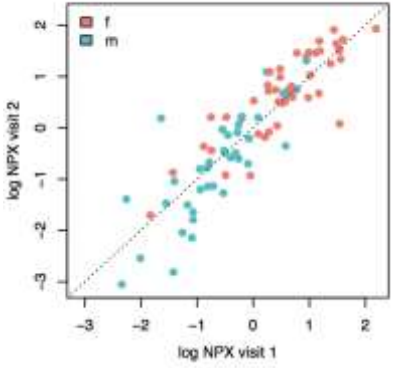
Leptin



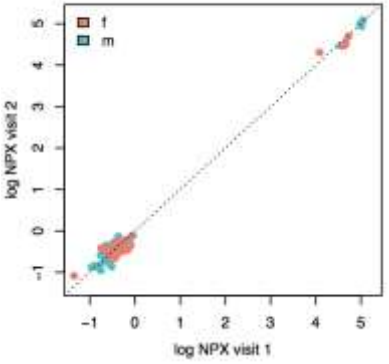
Folate Receptor 3



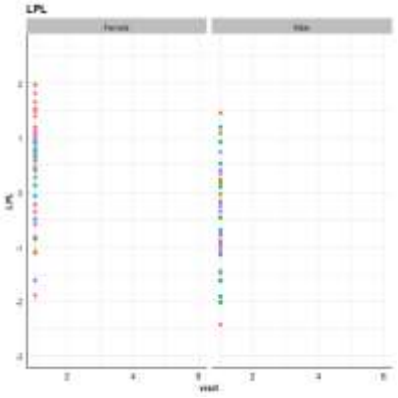
Leptin
r=0.89

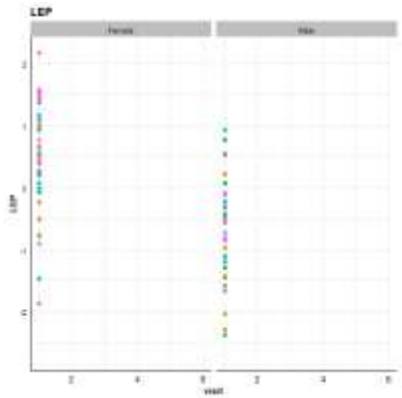


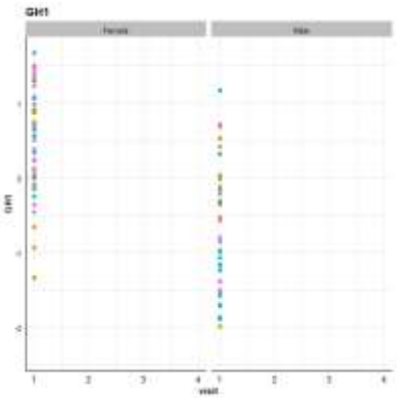
Folate Receptor 3
r=0.99

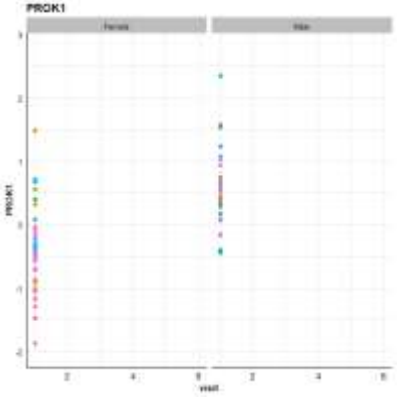


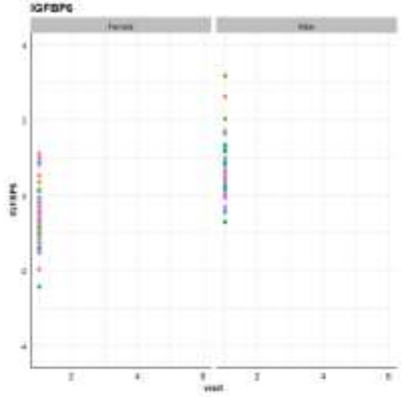
Wellness healthy cohort – protein examples

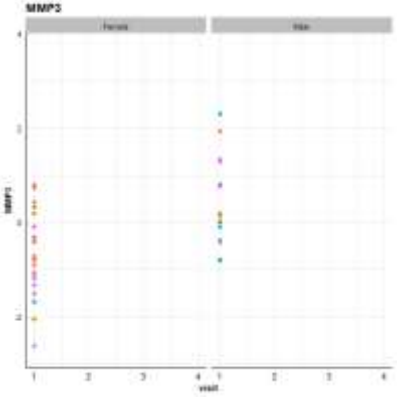






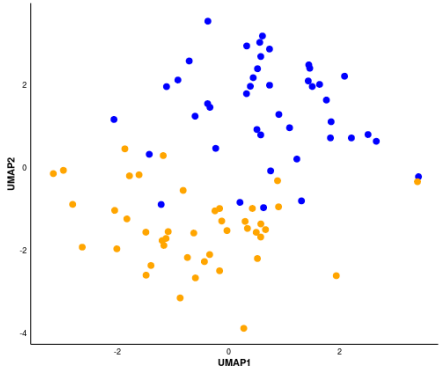




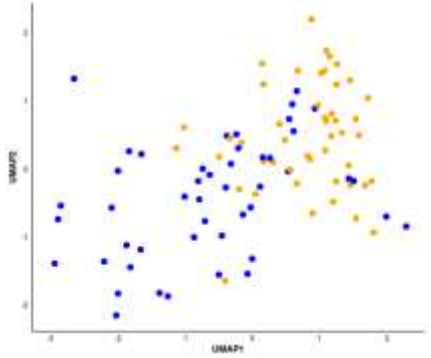


Longitudinal profiling of samples - UMAP

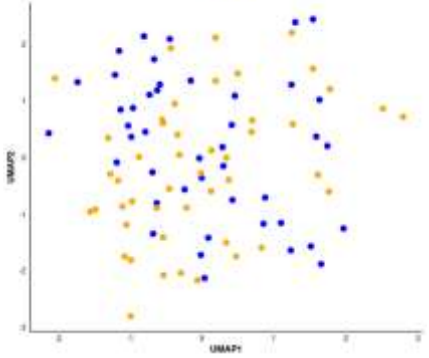
Proteome (n= 944)



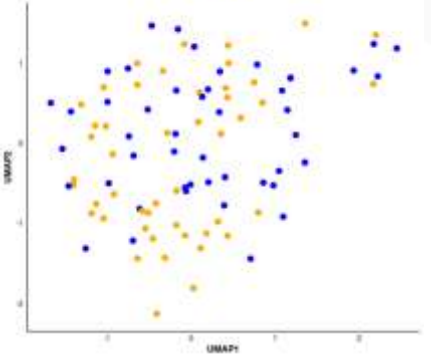
Clinical chemistry (n= 67)



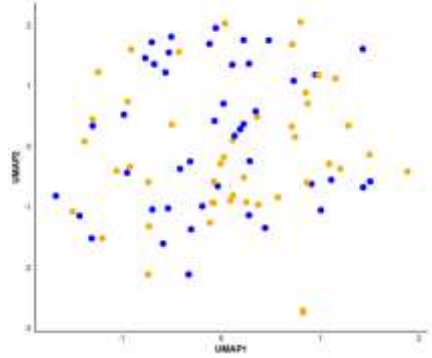
Autoantibodies (n= 1,456)



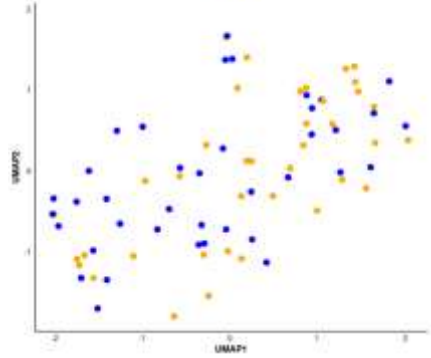
Metabolome (n= 133)



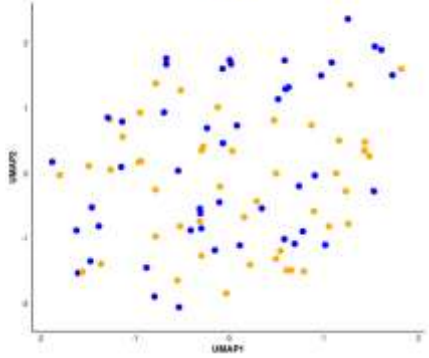
Microbiome (n= 1324)



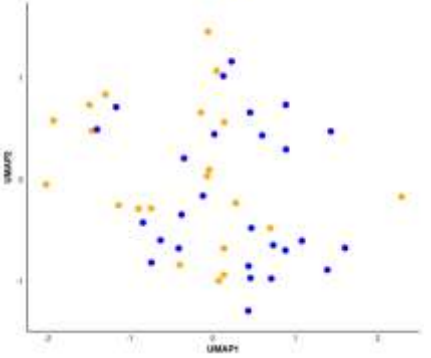
Transcriptome (n= 944)



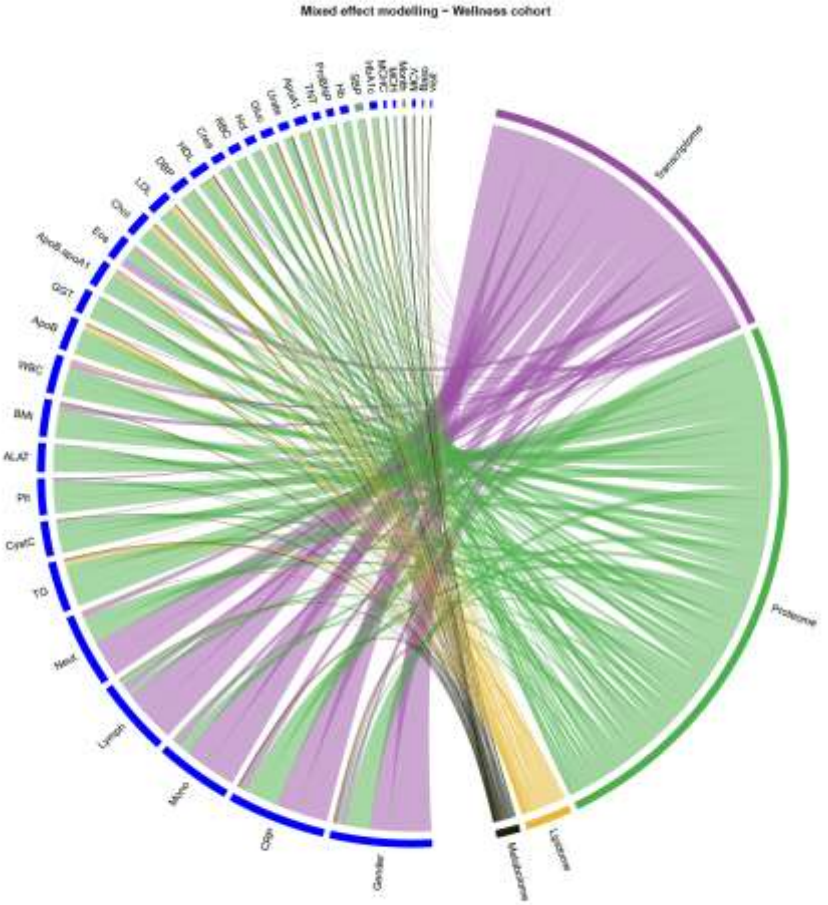
Immune cytome (n= 118)



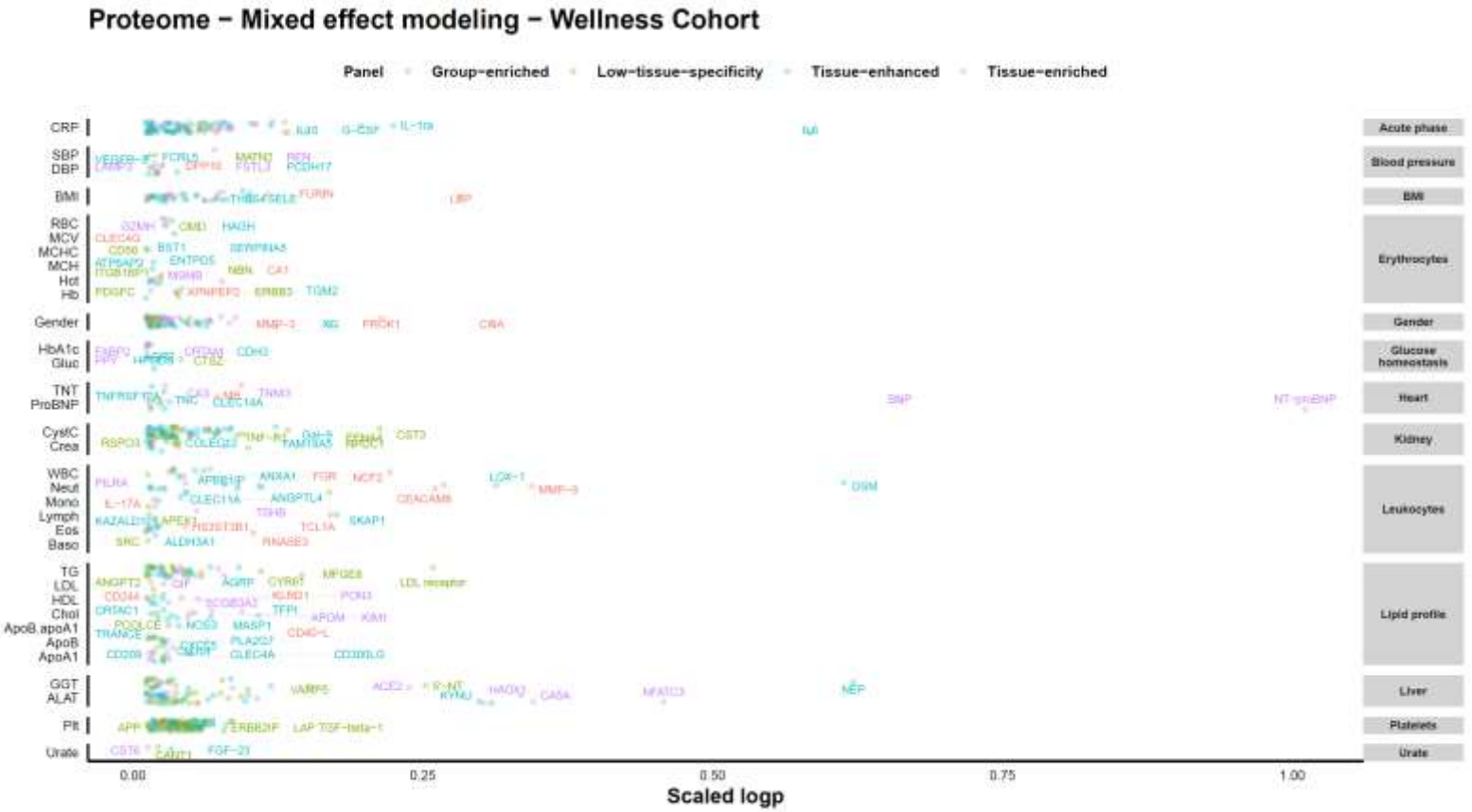
Lipidome (n= 87)



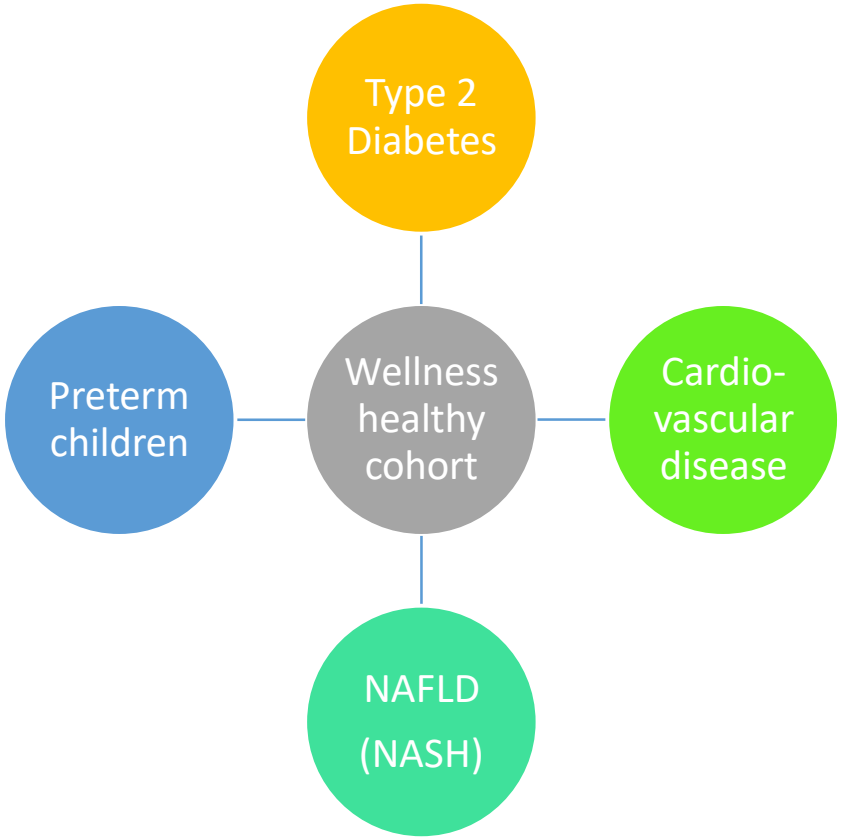
Wellness Cohort – Mixed effect Modeling

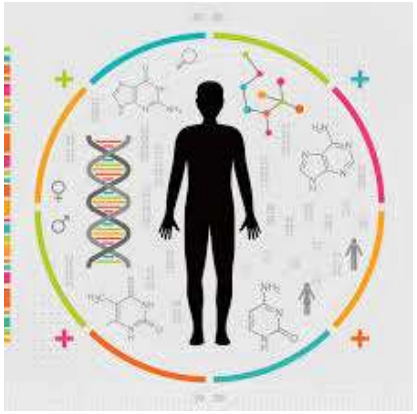


Olink data – mixed effect modelling



Precision medicine effort



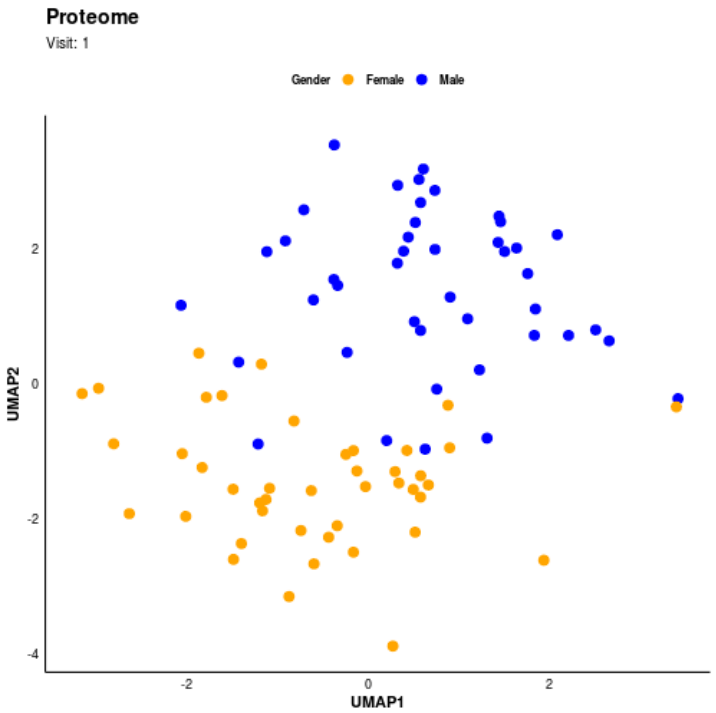


Type 2 Diabetes study

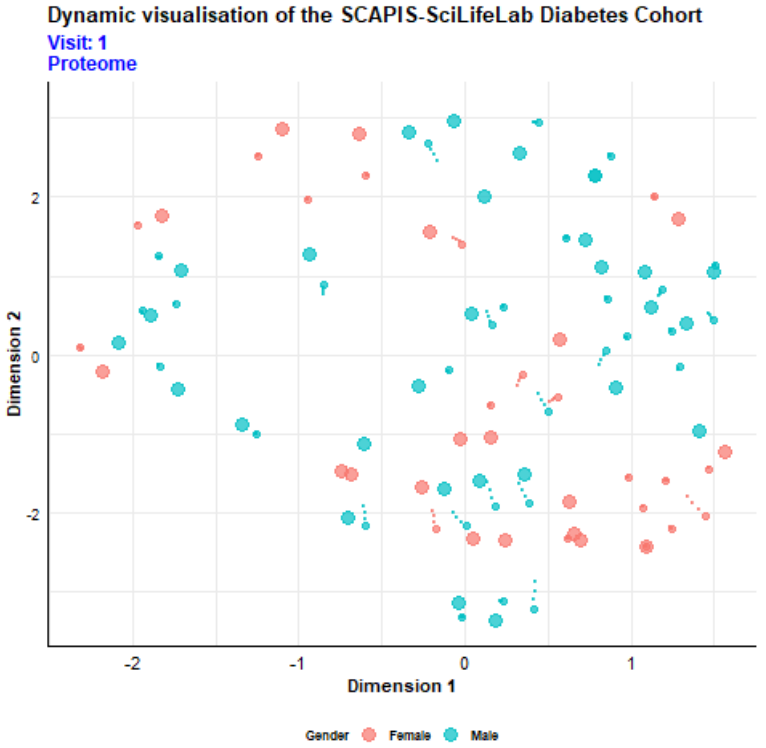
- Newly diagnosed T2D and treatment naïve at Visit 1
- Either elevated fasting glucose, elevated OGTT glucose, or both
- 52 subjects included (21 females and 31 males)
- 34/52 subjects were treated with metformin after Visit 1
- All were given lifestyle advice according to standard routine for T2D management

Healthy vs T2D – proteomics (Olink)

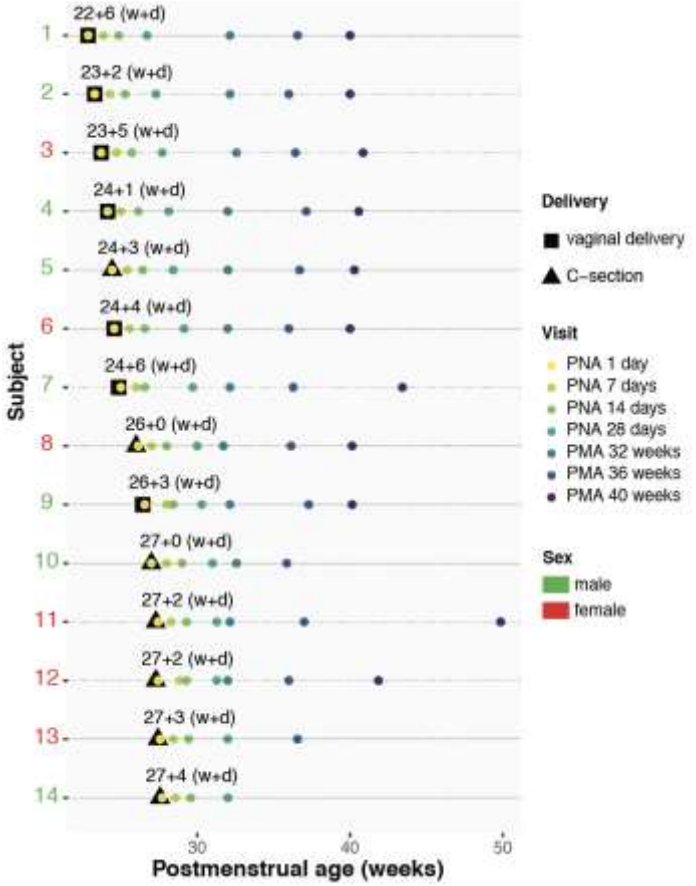
Wellness visit 1-6 (two years)



T2D visit 1-3 (three months)

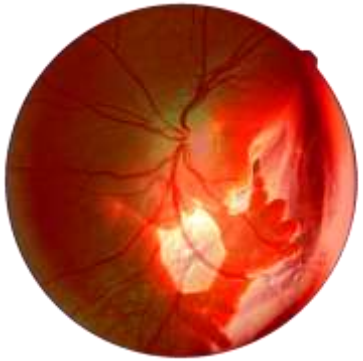


Longitudinal Integrated Profiling of Preterm Children



Cohort

- 14 neonates from ”Donna Mega” cohort from Queen Silvia Children's Hospital in Gothenburg, Sweden
- Samples collected 2013 – 2015
- Extremely preterm babies, gestational age 22-27 weeks
- Collected serum + feces



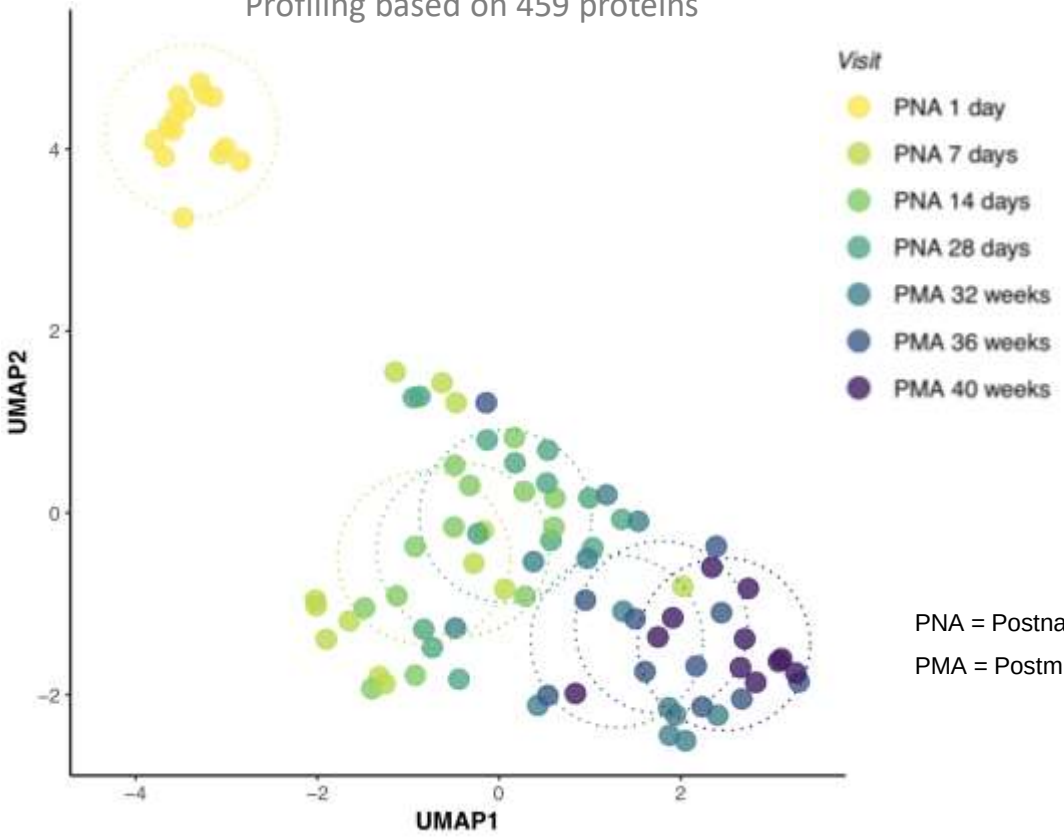
Blood samples:

#1: day 0 = cord blood
#2: day 1
#3: day 7 = 1 week
#4: day 14 = 2 weeks
#5: day 28 = 3 weeks
#6: gestation week 32
#7: gestation week 36
#8: gestation week 40

The Sahlgrenska Center for Pediatric Ophthalmology Research

Longitudinal Integrated Profiling of Preterm Children

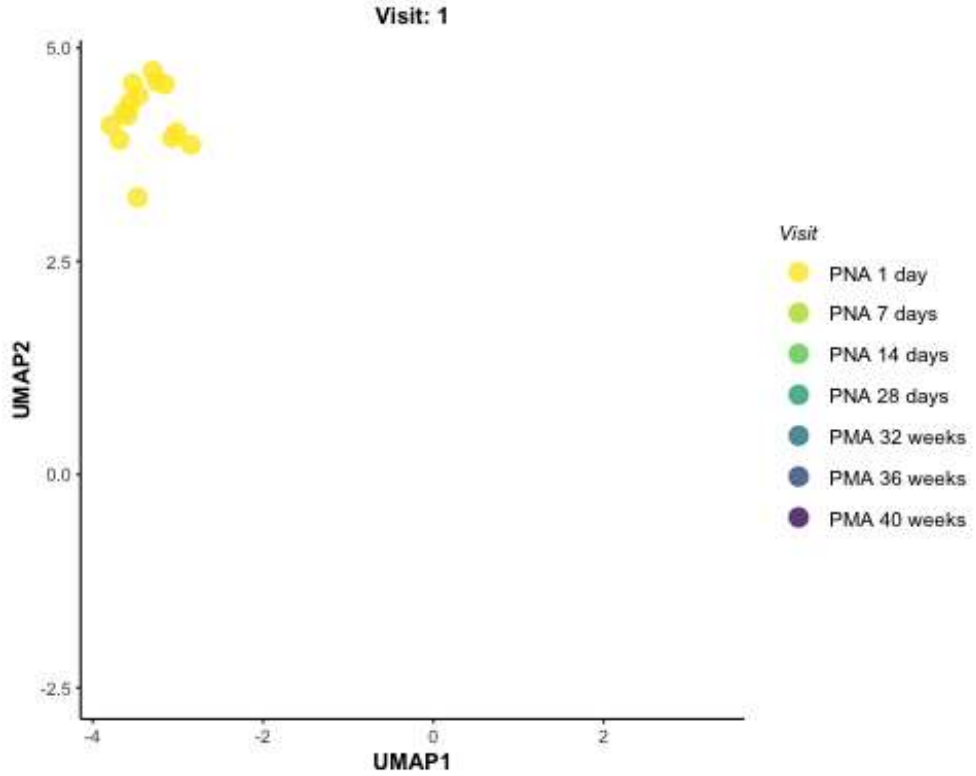
Profiling based on 459 proteins



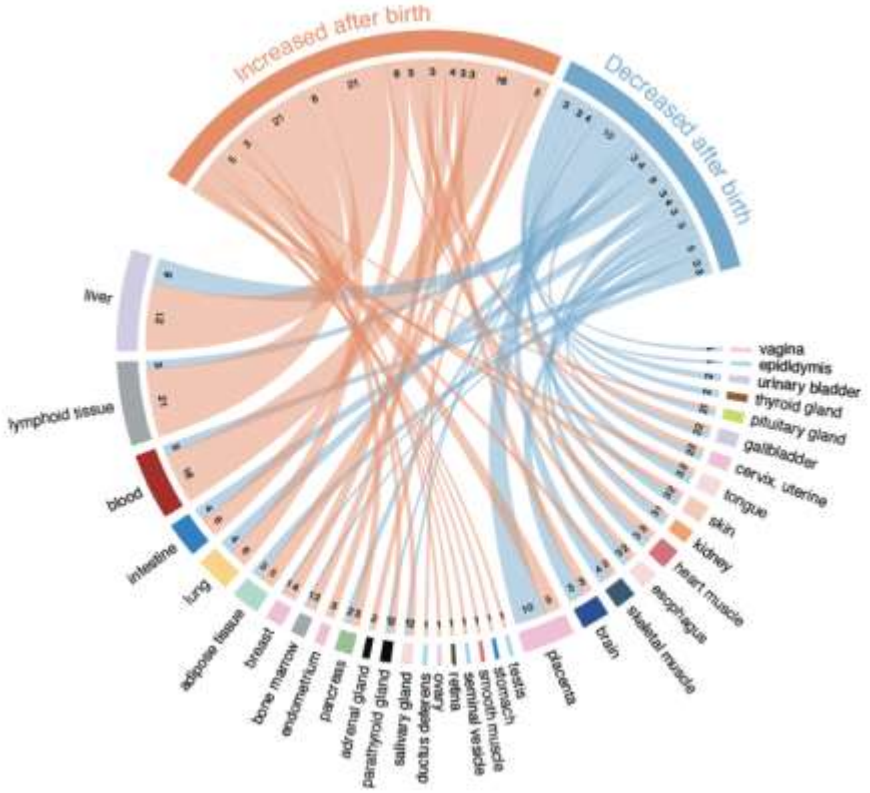
PNA = Postnatal age

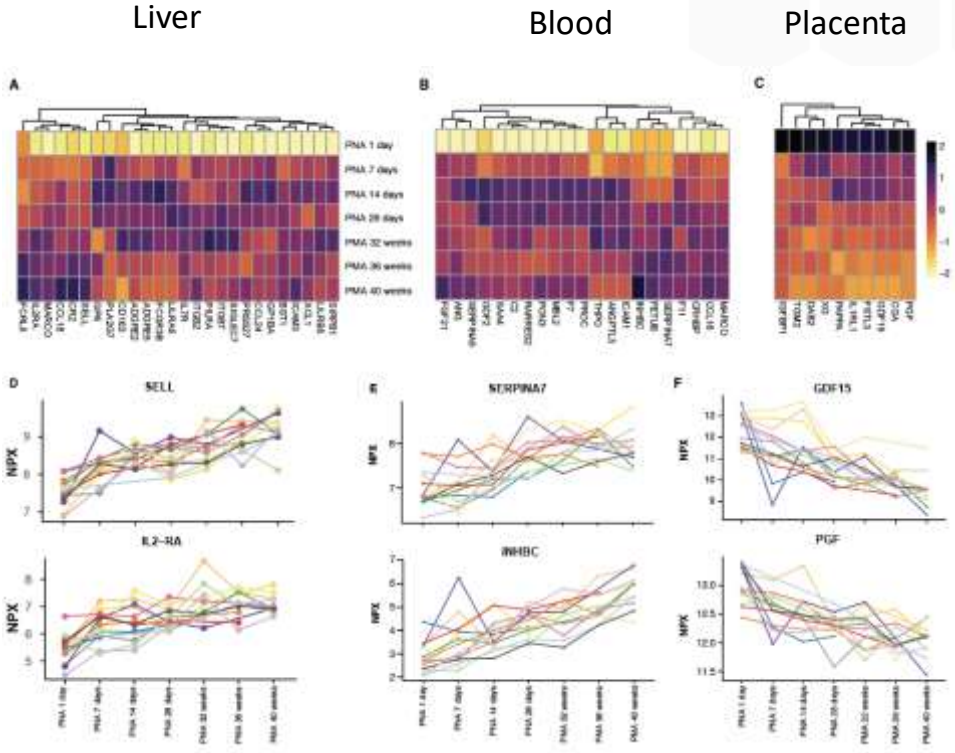
PMA = Postmenstrual age

Longitudinal Integrated Profiling of Preterm Children

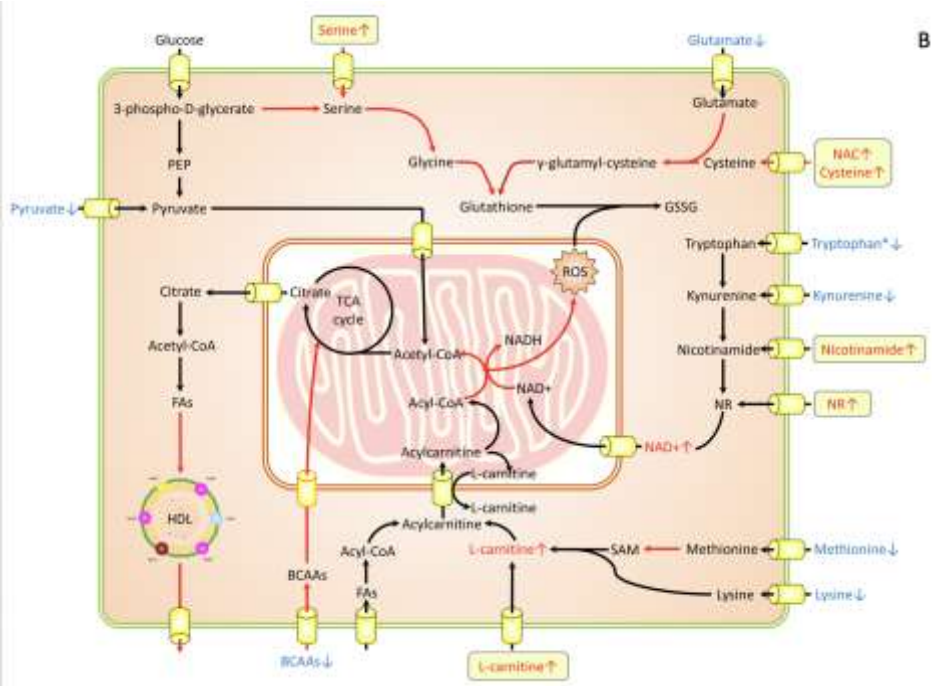


Longitudinal Integrated Profiling of Preterm Children





Fat liver disease (NAFLD) – clinical trial



A

20 g serine
3 g L-carnitine
5 g NAC
1 g NR

Calibration study
Metabolomics and proteomics analysis
Genome-scale modelling
PB-PK Modelling
Dose adjustment

12.35 g serine
2.55 g L-carnitine
2.55 g NAC
1 g NR
Twice daily

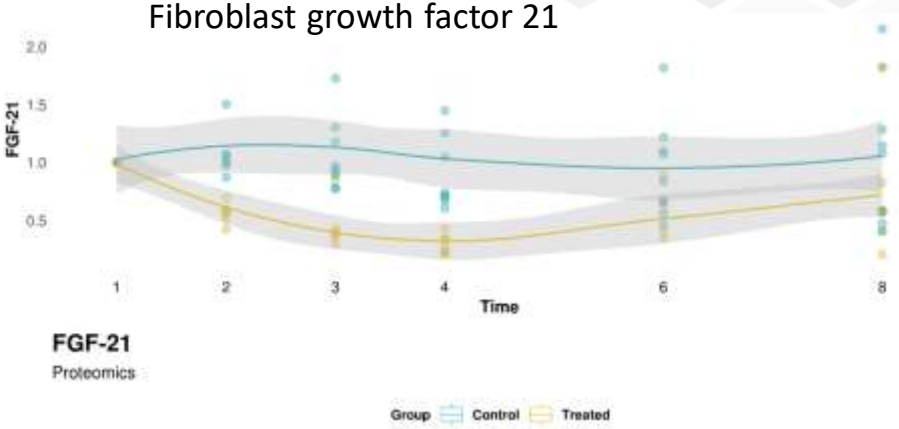
	Breakfast	T0	T1	T2	T3	T4	T5	T6	T7
Supp. (9 subjects)	7:00	8:00	9:00	10:00	11:00	12:00	13:00	14:00	15:30
Control (10 subjects)	7:00	8:00	9:00	10:00	11:00	-	13:00	-	15:30

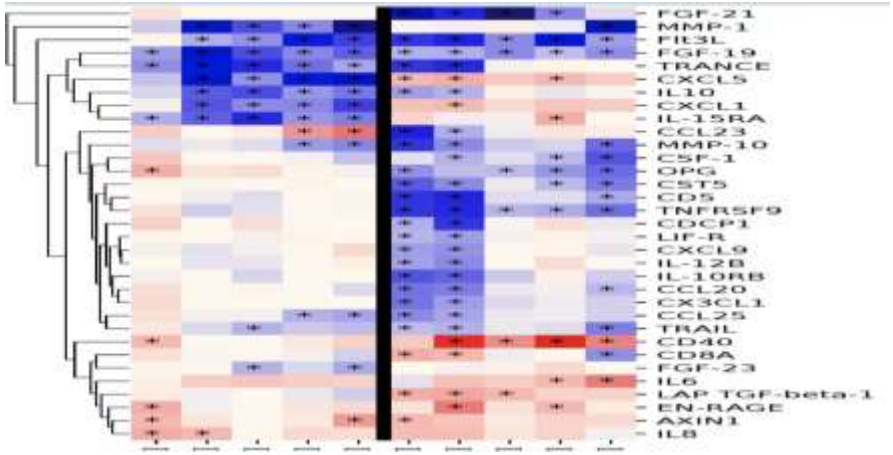
Adil Mardonpglu
Jan Boren

ScandiBio Therapeutics

Fat liver disease (NAFLD) – clinical trial

Fibroblast growth factor 21





Functions as a major metabolic regulator. The protein stimulates the uptake of glucose in adipose tissue.

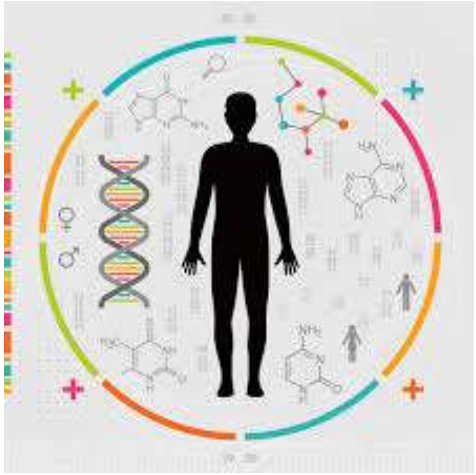
Control

Treated

Moved to phase 2 clinical trials

Take-home messages

- Protein profiling very important tool for precision medicine
- New tools for comprehensive and quantitative protein profiling
- Each healthy individual has a stable and unique protein profile
- Dramatic changes upon life style changes (and health changes)
- Dramatic changes upon drug treatment
- Dramatic changes in the pre-term babies



Multi-omics integration and wellness profiling

Linn Fagerberg

Group leader

Abdellah Tebani

Post-doc

Wen Zhong

Post-doc

Max Karlsson

PhD student

Division of Systems Biology
Department of Protein Science
Science for Life Laboratory
KTH Royal Institute of Technology

Mission:
to perform integrative omics analysis based on precision medicine data as well as the Human Protein Atlas

5.

Concluding remarks

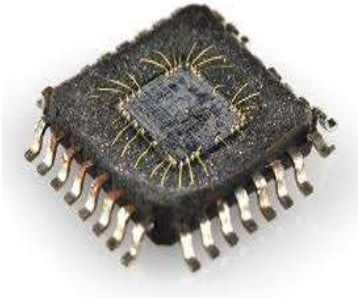
Mapping of human building-blocks

Initiative	Funding
Human Protein Atlas (Europe/Asia)	Wallenberg Foundation
Allen Brain and Cell Atlas (USA)	Paul Allen (Microsoft)
Human Cell Atlas (US and Europe)	Chan-Zuckerberg (Facebook)
Project Baseline - Verily (USA)	Google
Watson Health (USA)	IBM

Society-changing innovations

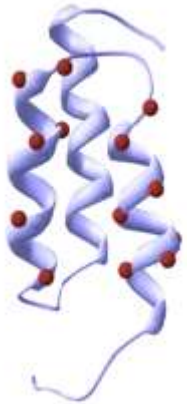
Technology:

- Integrated circuits (70:ies)
- Internet (90:ies)
- Smart phones (00:ies)
- Artificial intelligence
- Solar panels for electricity



Life science

- Gene technology (80:ies)
- Biological drugs (00:ies)
- “Next generation” precision medicine
- Mapping the building-blocks of humans



Future – Measurable Man

Will we (in the future) be able to construct a digital model of humans - covering cells, tissues, organs and diseases ?

Will we (in this case) be able to construct a “digital twin” of everybody (patients) to test the efficacy of drugs digitally (on an individual basis) before decision on therapy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Åsa Sivertsson
Kalle von Feilitzen
Per Oksvold
Jan Mulder
Evelina Sjöstedt
Åsa Sivertsson
Jens Nielsen
Emma Lundberg
Fredrik Edfors
Adil Mardinoglu
Tomas Hökfelt
Peter Nilsson
Sophia Hober
Hanna Tegel
Jochen Schwenk
Johan Rockberg
Fredrik Ponten
Peter Thul
Martin Zwalen
Petter Brodin
Cheng Zhang
THE HUMAN PROTEIN ATLAS

Science for Life Laboratory

SciLifeLab

A national infrastructure for next-generation life science

Global trends:

Need for major infrastructures

Technology evolving rapidly

Big data

UPPSALA UNIVERSITET

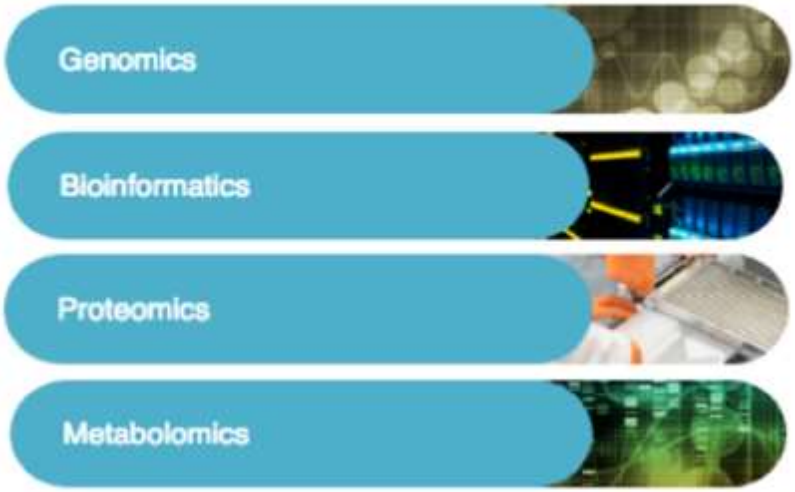
Karolinska Institutet

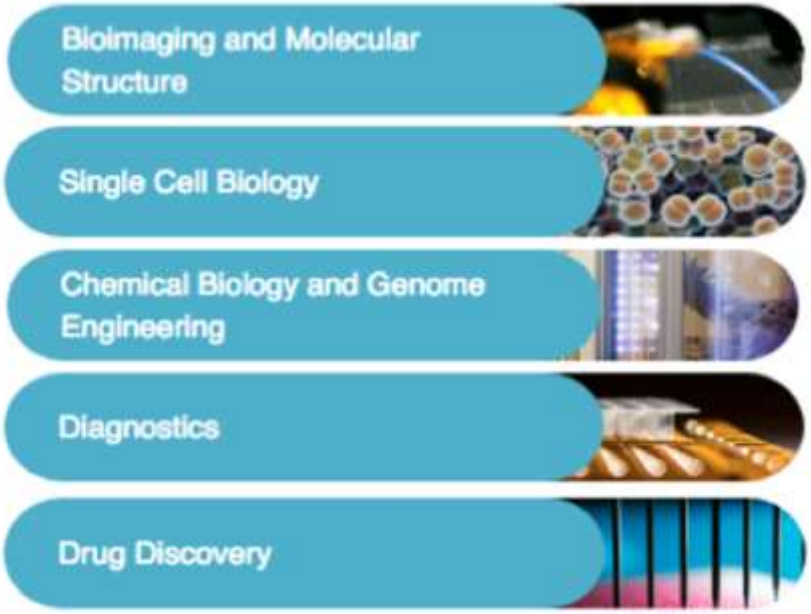
Stockholm University

KTH VETENSKAP OCH KONST
ROYAL INSTITUTE OF TECHNOLOGY

Infrastructure resource for integrative omics

SciLifeLab



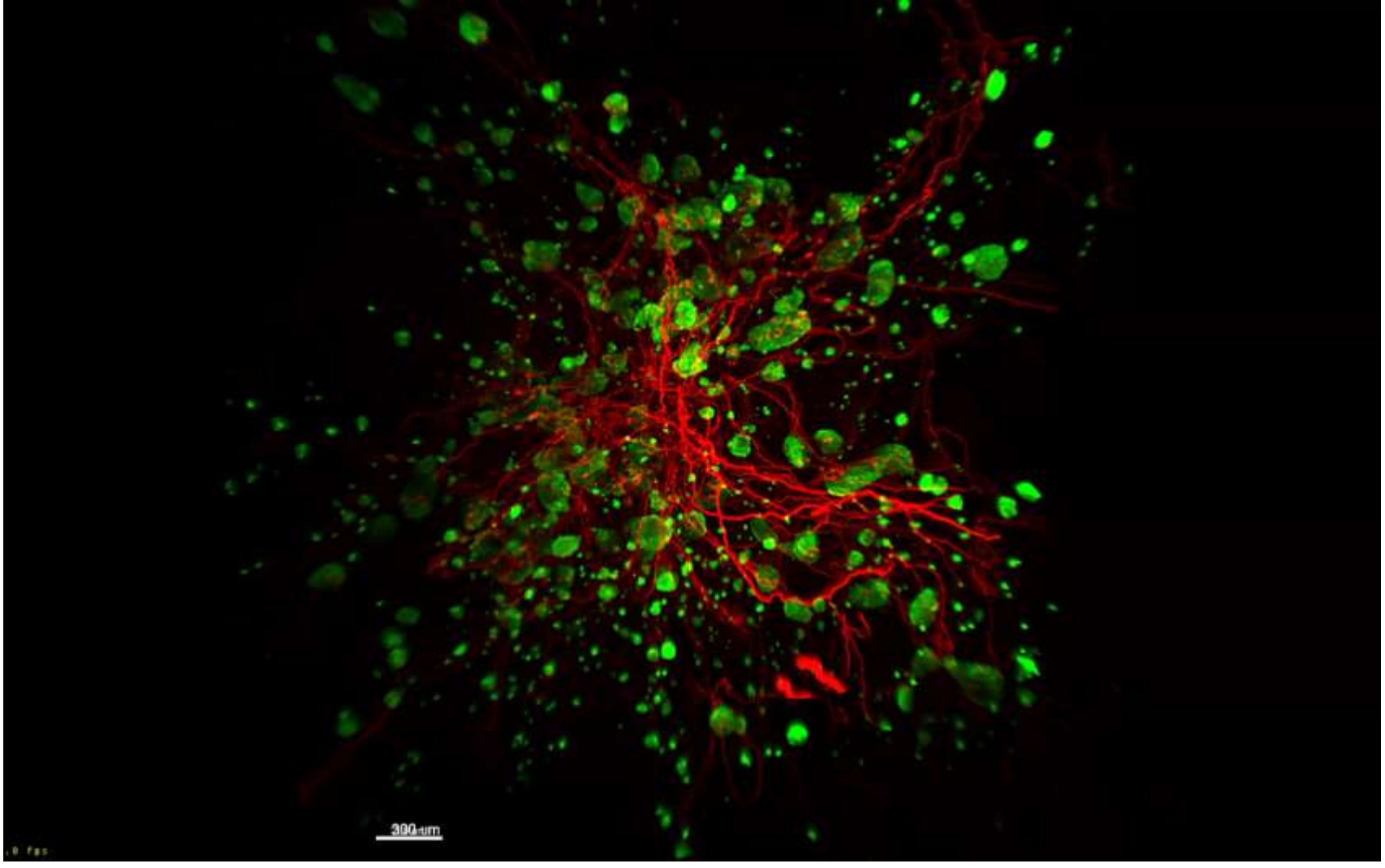


- **Started in 2013**
- **1 200 researchers**
- **More than 3000 projects in 2018**

Funding

- Wallenberg Foundation (Human Protein Atlas project)
- Novo Nordisk Foundation (Center for Biostainability)
- Erling Persson Foundation (Precision medicine)
- Heart and Lung Foundation (Biobank profiling)
- Chan Zuckerberg Foundation (Human Cell Atlas)
- ELIXIR – sharing of data resources


Stockholms universitet
KTH
SciLifeLab
Karolinska Institutet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