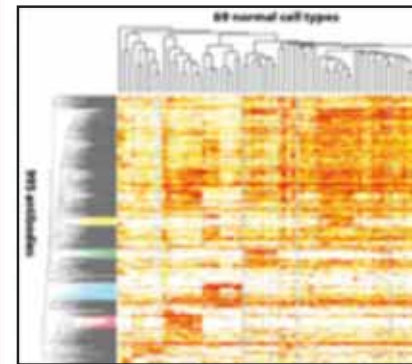
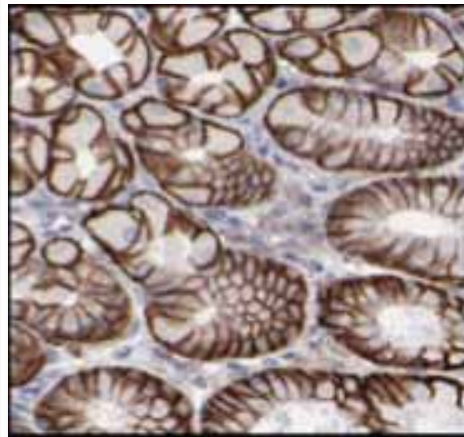
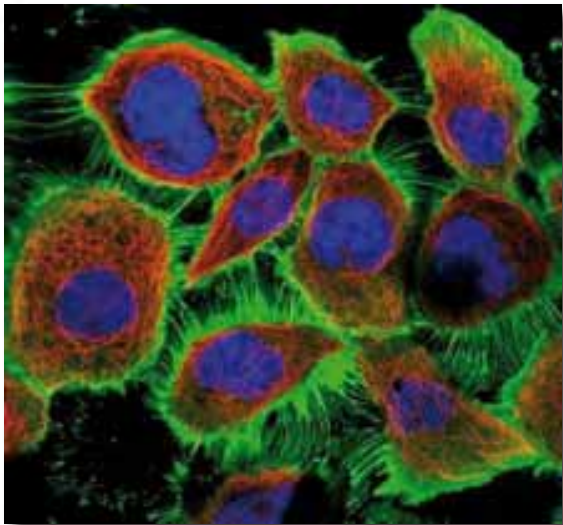


Individualiserad behandling – var är vi och vart ska vi ?



Blicka seminarium, November 11, 2010

Prof Mathias Uhlen
Science for Life Laboratory
Royal Institute of Technology (KTH)
Stockholm, Sweden

The Science for Life Laboratory - Stockholm

SCIENTIFIC FACILITIES

Sweden Bets on New Lab to Spruce Up Its Bioscience Future

The next hours the state of a neighbor—Norway spruce (Picea abies)—has this center is central to Sweden's forest health. It tests the nation's vigorous timber industries and by some estimates is economically the country's most important species. To a major sequencing effort the Swedish Board of Agriculture and the Swedish Environment for year announced it would provide about \$100 million for the sequencing of the Norway spruce's genome. But what is unexpected—or at least it would have been a surprise—is that this sequencing will largely happen in Sweden rather than being limited out to other countries. Here, such, officials in Stockholm will inaugurate a new building with cutting-edge DNA sequencing machines that by 2011 should produce a rough draft of the genome of the "Christmas" tree.

For Sweden, this building represents the next phase of a single research project. It's the most visible evidence to date of the Science for Life Laboratory (SciLifeLab), an unusual initiative spanning multiple Swedish research organizations and four sites, one in Stockholm and the other in nearby Uppsala. Rather than spread its money to so many scientific projects, as it has traditionally done, the Swedish government will spend more than \$75 million setting up SciLifeLab with the hope that it will become a technology-driven national life sciences center, comparable to organizations such as the Broad Institute in Cambridge, Massachusetts. "We want to make sure [the latest] technologies are available to all of Sweden. It's a deliberate decision to do things differently," says genomicist Kersti Lindahl-Falk, who is the director of SciLifeLab's Uppsala office and has a previous work with the Broad Institute.

The dream of creating a national research center in biology has been abandoned for years by officials at the Karolinska Institute, Stockholm University, and the Royal Institute of Technology (KTH), all in Stockholm. But it only became a reality when the Swedish government recently offered major strategic research grants for several life sciences fields. The three institutions banded together last year to win the lion's share of the "strategic-biosciences" money and then joined with Uppsala University, another grant winner, to form SciLifeLab.

By 2011, the building in Stockholm



Center of attention: 2010 a new facility in Stockholm spruce's forest that will sequence the Norway spruce genome. Sweden's Science for Life Laboratory aims to become a national life sciences center.

SciLifeLab's DNA sequencing output will be only about 60% of that of the Wellcome Trust Genome Campus in Hinxton, U.K. For example, that Sweden is working on an unprecedented marriage of genomics with performance to set it apart. Uppsala University and the Royal Institute of Technology are already home to a project, the Human Protein Atlas, that by 2014 intends to create antibodies to identify every human protein. SciLifeLab "will be the only lab with antibodies to all human proteins and the ability to sequence human genomes. It's a unique niche," says KTH's Mikael Lindblom.

Scientists say they will see antibodies from the Human Protein Atlas to examine individual locations of human proteins, for example. And there are plans to analyze the Baltic Sea ecosystem, says KTH's Malin Ekblom, who leads the Human Protein Atlas and Stockholm's SciLifeLab. Lindahl-Falk says the Uppsala site will add its strengths in comparative genomics and evolutionary biology to the mix.

—JENNIFER HADLEY

NEWS OF THE WEEK

For now, the Norway spruce is central stage. The center has had its genome sequenced, in part because they typically are full of repetitive DNA sequences. Norway spruce and its human genome likely have comparable gene numbers, but the future is unclear. It may trigger "It's one of the largest, most complicated genomes to be sequenced," says Phil Stevenson of Uppsala University, who leads the spruce project. "We want to identify genes that control wood properties."

SciLifeLab's partnership with Uppsala in the spruce genome is a first step toward connecting Swedish scientists outside Uppsala and Stockholm that the project is the first as well. "Most cooperation in Sweden are waiting to see if we can deliver useful information for them. It's up to us to give to you," acknowledges Ekblom.

Downloaded from www.sciencemag.org on May 17, 2010

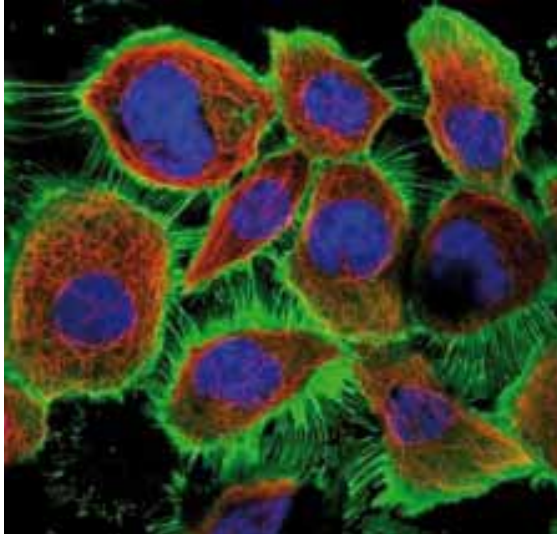
www.sciencemag.org SCIENCE VOL 328 14 MAY 2010

805

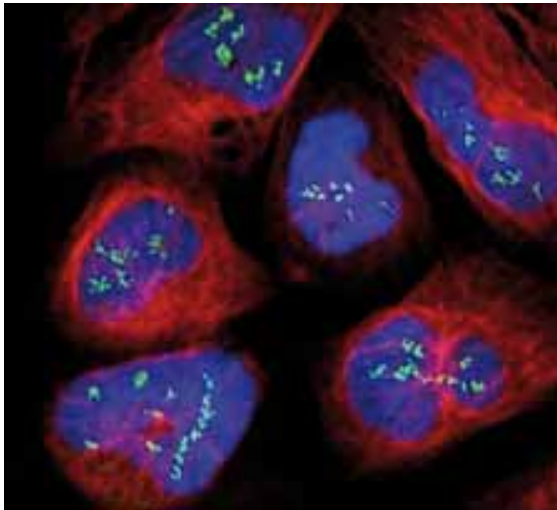
- New resource center for high-throughput bioscience
- Joint effort of three universities (Karolinska, KTH and SU)
- May 2010. Start of center. 150 researchers in 2011.
- Next generation sequencers
- Next generation plasma/serum profiling
- Worlds largest collection of antibodies to human targets

Science 328,805 (14 May 2010)

Outline



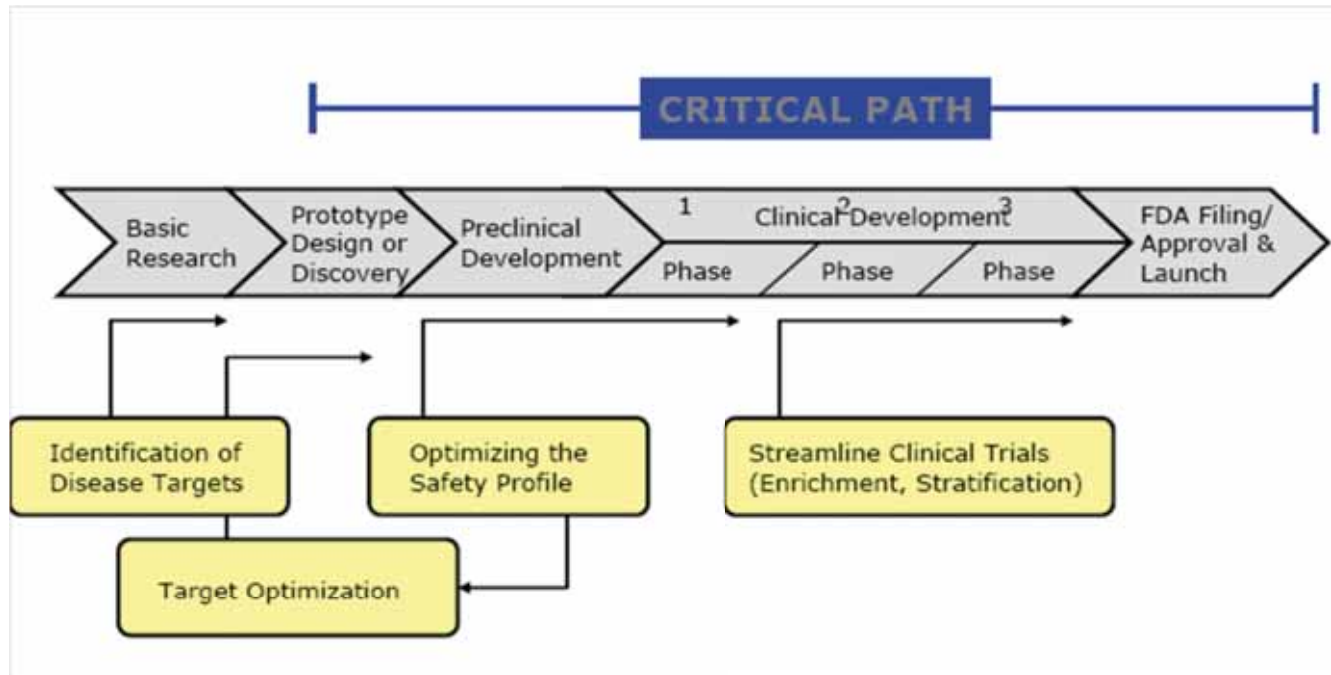
1. Individualized therapy – introduction
2. The human genome project – status
3. The Human Protein Atlas project
4. Personalized medicine
5. Future prospects



1

***Individualized medicine – an
introduction***

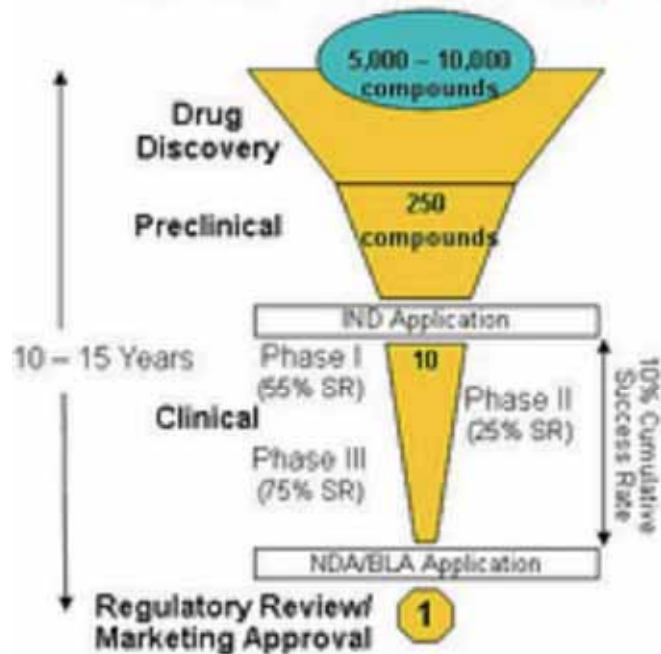
Drug development



- Very expensive clinical trials (altogether 1 billion USD in cost)
- High failure rates in all phases

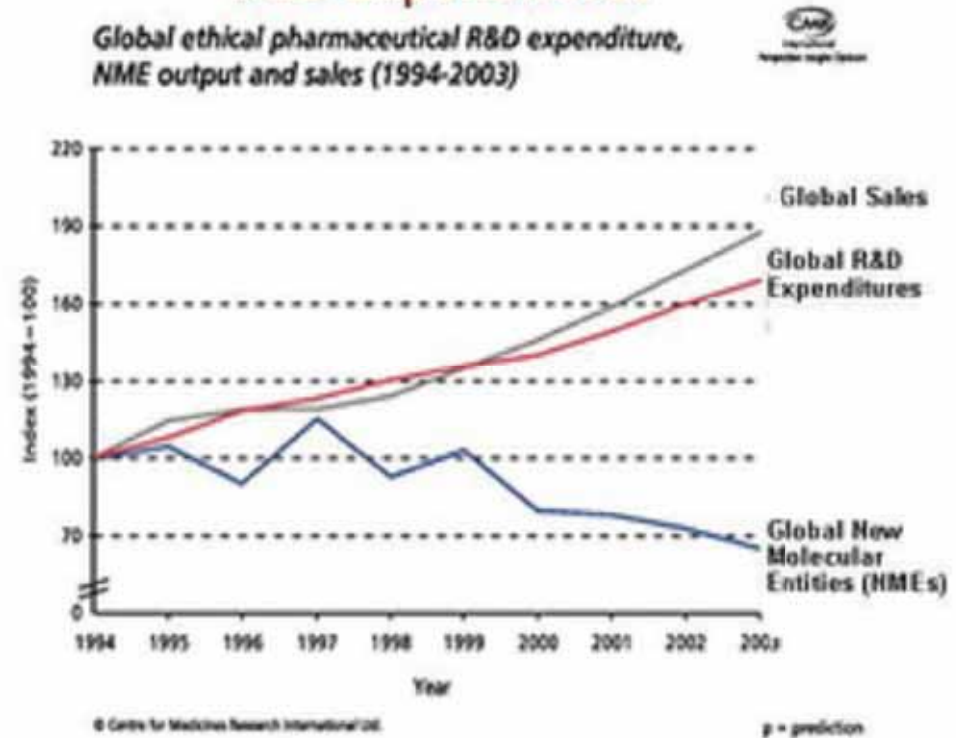
Dramatic decline in productivity

Attrition Remains Very High



Output Not Keeping Up With R&D Expenditures

Global ethical pharmaceutical R&D expenditure, NME output and sales (1994-2003)



Source: PhRMA, CMR, Genentech, Booz Allen Hamilton: *The Global Innovation 1000*, 2006

Personalized medicine

Traditional pharmaceutical drug

- An average drug to an average patient
- Find optimal dose with good efficacy without serious side-effects

Individualized drug treatment

- An individual treatment to an individual patient
- Stratify patients into responders and non-responders
- Develop diagnostic test for choice of treatment (or dose)
- Avoid treatment of patients which will have serious side-effects

2

The human genome project

Kunskap om vår värld

- 1700-talet - Biologins systematik (Linné)
- 1800-talet - Kemins systematik (Berselius)
- 1900-talet - Fysikens systematik
- 2000-talet - Medicinens systematik

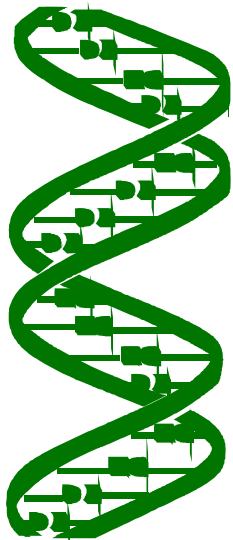
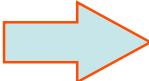
Livets byggstenar

A
C
A
G
T
T
A
C

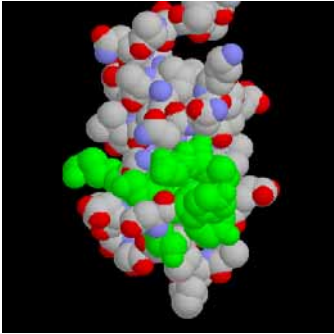
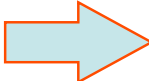
— — — — — — — —

T
G
T
C
A
A
T
G

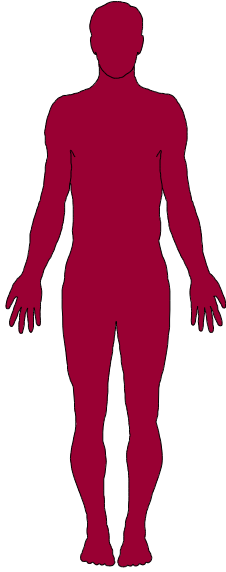
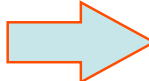
Baser



DNA



Proteiner



Organism

Molekyl

DNA

Protein

Information

“Digital”

“Analog”

Funktion

Minne

Livets kemi

Byggsten

4 baser

20 aminosyror

"Genomikens" historik

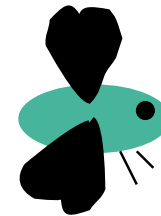
 1995 - första bakterien

 1996 - jästsvamp

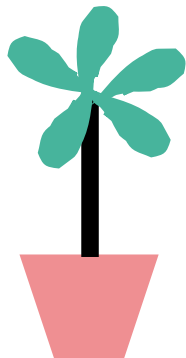


 1998 - rundmask

 1999 - bananfluga

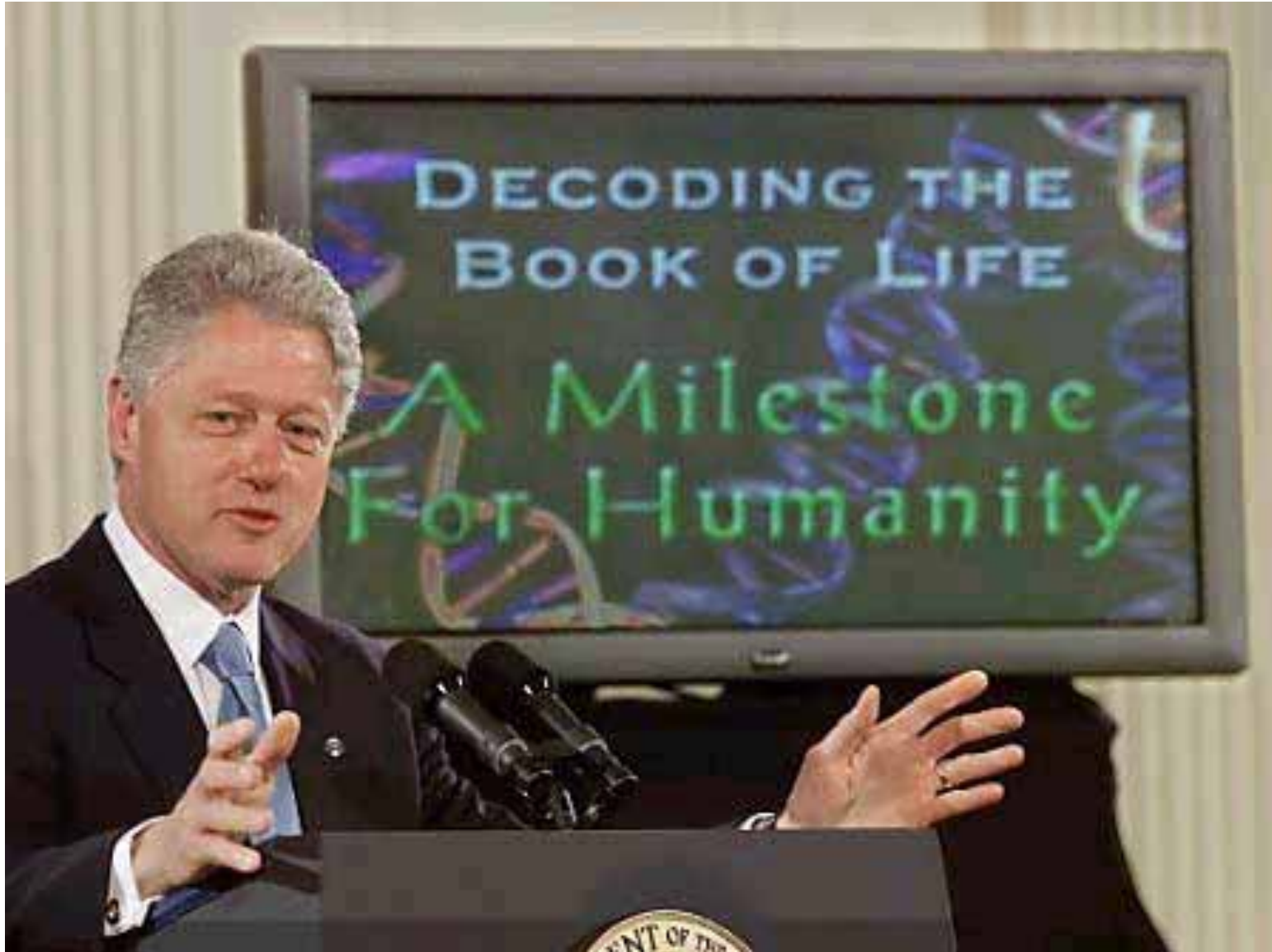


 2000 - första växt (backtrav)



 2001 - människan

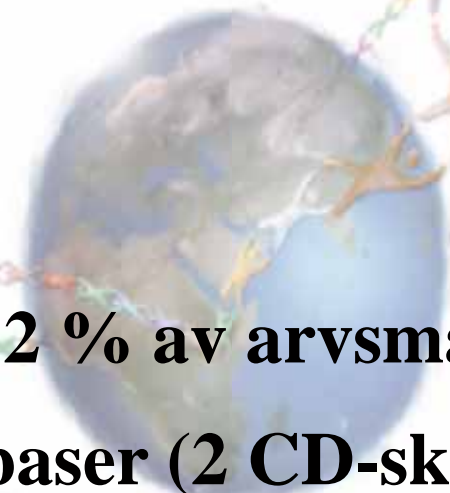
Läsa livets bok - en milstolpe för mänskligheten



Vita huset, Washington, juni 2000

Kartläggning av människans arvs massa

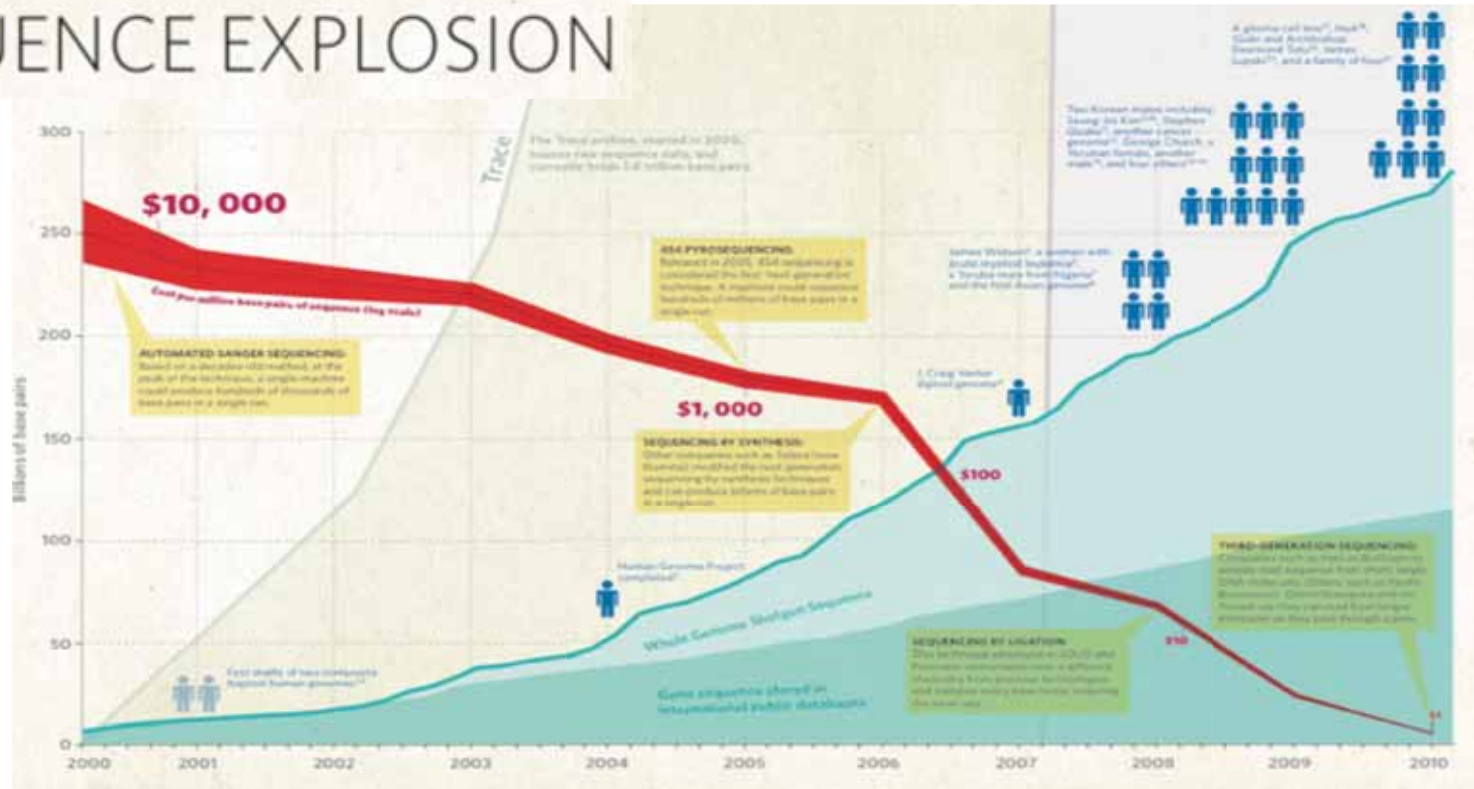
- **Juni 2000 ("komplett sekvens") - 141, 821 gap**
 - **Februari 2001 ("färdig sekvens")**
 - **April 2003 ("mer komplett sekvens")**
 - **Augusti 2007 ("även mer komplett sekvens") - 120 gap**
-
- **Antal gener: 20,000 (ca 2 % av arvs massan kodande)**
 - **Varje cell: 6 miljarder baser (2 CD-skivor)**



the
Human
Genome

Next generation sequencing

SEQUENCE EXPLOSION



Pyrosequencing: Ronaghi, Uhlen & Nyren (1998) Science 281, 363-365.

NATI, 02/04/2011 April 2010

Långsiktigt mål: sekvensen för en människas arvsmassa för 1 kUSD

Personalized genomics



Generated with 454
(pyrosequencing)

Published online 1 June 2007 | Nature | doi:10.1038/news070528-10

News

James Watson's genome sequenced

Discoverer of the double helix blazes trail for personal genomics.

Erika Check

Nobel laureate James D. Watson peered deep into his genome yesterday. And soon, anyone else interested in his genetic makeup will be able to do the same.

Scientists in Houston presented Watson with a DVD of his genome sequence, which they said was the "first individual genome to be sequenced for less than \$1 million". The carefully worded claim may be an acknowledgement that another personal genome project has already been completed: J. Craig Venter has deposited his genome sequence into the public GenBank database, he told *Nature* two weeks ago.

Such personal genomes are for now largely symbolic, because it's difficult to draw concrete information about a person's health from his or her genome sequence.



James Watson is the first individual sequenced for less than million.

*National Library of
Medicine*

Arvsmassan hos Neanderthal

The New York Times

Scientists Plan to Rebuild Neanderthal Genome



Jan Wolke/European Pressphoto Agency

From left, Michael Egholm, Svante Paabo and Ralf W. Schmitz showing an original cast of a Neanderthal bone.

By NICHOLAS WADE
Published: July 20, 2006

Researchers at the Max Planck Institute for Evolutionary Biology in Leipzig, Germany, plan to reconstruct the genome of Neanderthals, the archaic human species that occupied Europe from 300,000 years ago until 30,000 years ago until being displaced by modern humans.

The genome will initially be reconstructed using DNA extracted from Neanderthal bones that are 45,000 years old, which were found in Croatia, though bones from other sites may be analyzed later.

The project is a collaboration between Dr. Svante Paabo of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, and 454 Life Sciences, a Connecticut company that has developed a new method of sequencing, or decoding, DNA.

S
T
E
A
C

Från genetiska markörer till behandling av patienter



Varför blir man sjuk ?

- Genetik (arv)
- Miljö
- Ålder
- Slump

Proteiner - livets kemi

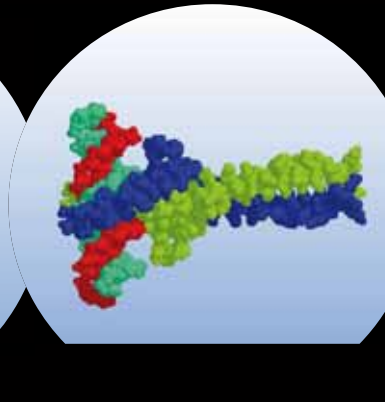
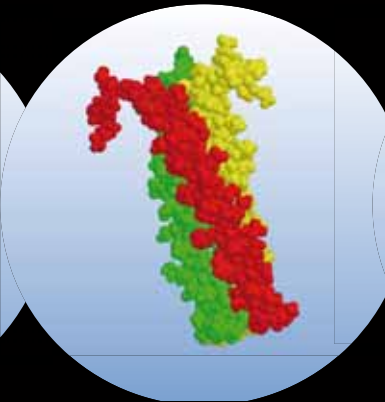
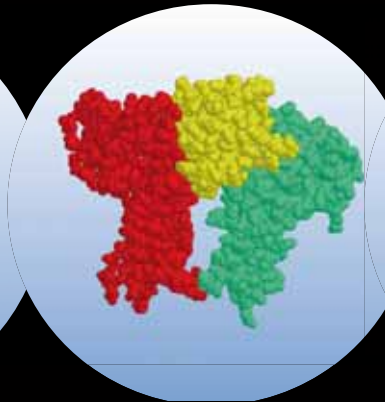
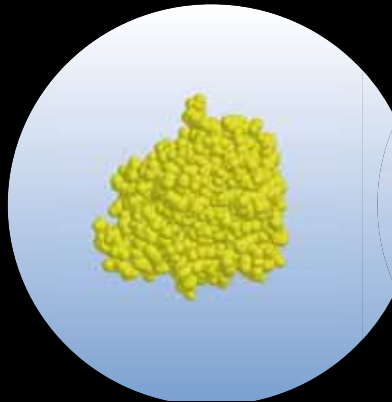
Katalys

Signalering

Struktur

Reglering

Skydd



Enzym

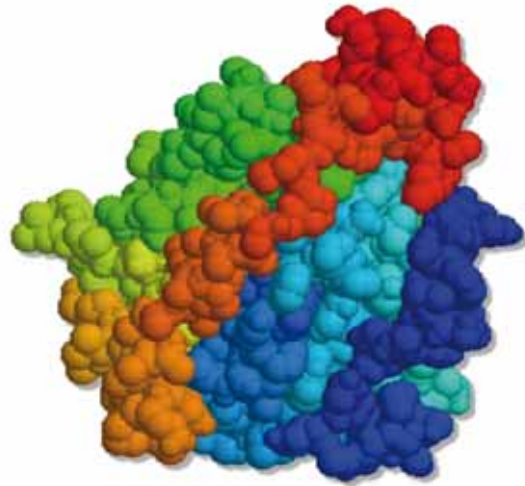
Hormon /
Receptor

Collagen

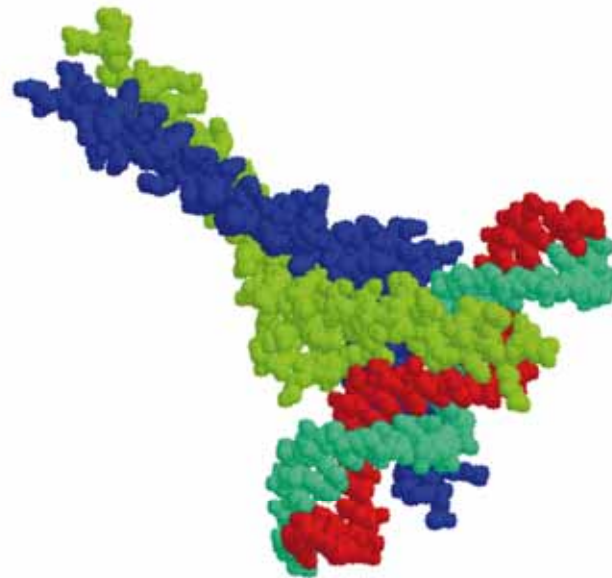
DNA-bindande
protein

Antikropp

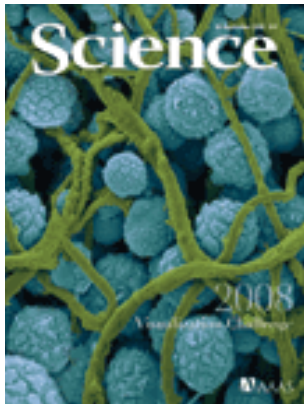
Proteiner - mål för nästan alla läkemedel



Mål för läkemedel	%
Enzymer	28
Receptorer	45
Hormoner	21
Nukleära receptorer	4
Totalt (proteiner)	98

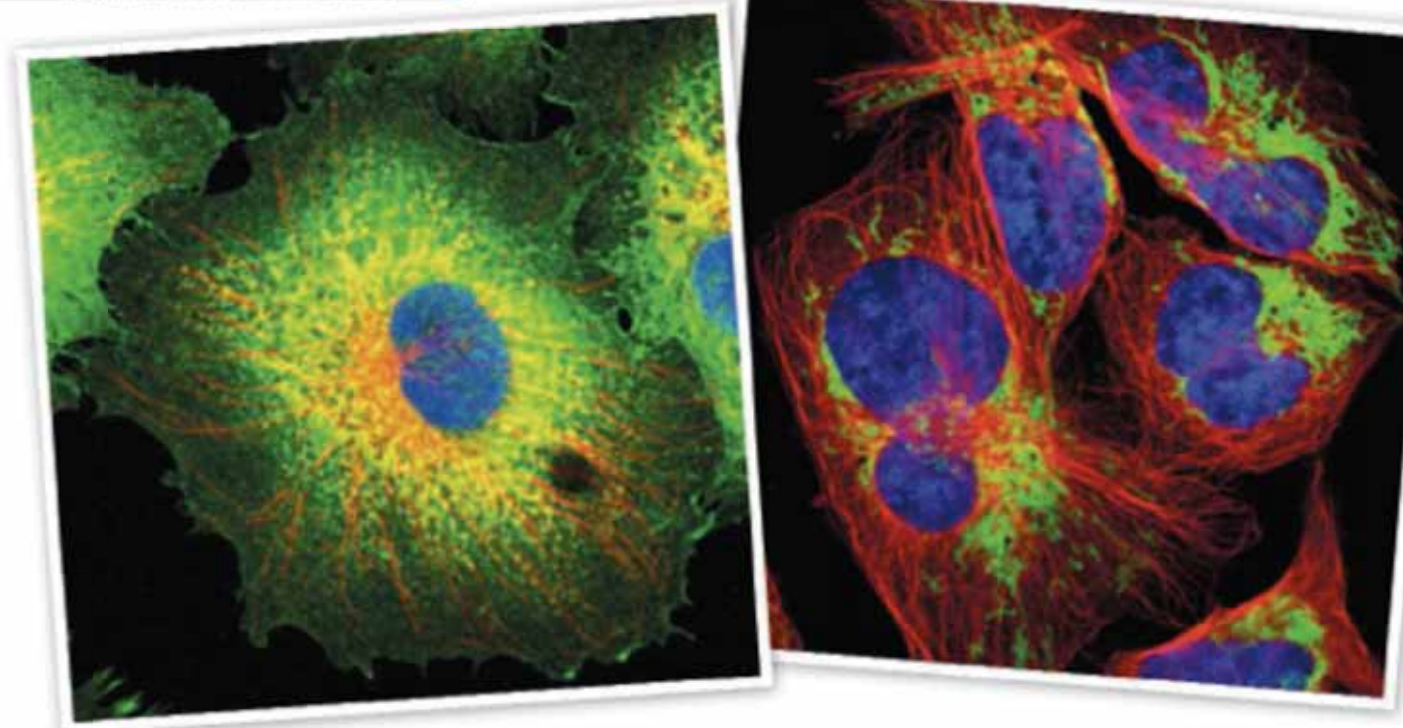


Mapping the building blocks of life



26 SEPTEMBER 2008
VOL 321
PAGES 1758-1761

NEWSFOCUS



Proteomics Ponders Prime Time

Improved technologies for tracking thousands of proteins at once have spawned talk of a full-scale project to reveal all the proteins in each tissue—but the price tag would be daunting

It's not just talk. Uhlen and other proteomics leaders gathered here last month to weigh plans for an HPP and to sound out representatives of science funding agencies that would need to pony up the hundreds of mil-

3

The Human Protein Atlas project

The Human Protein Atlas project team

KTH, Stockholm (main site)

• *Uppsala University (clinical site)*

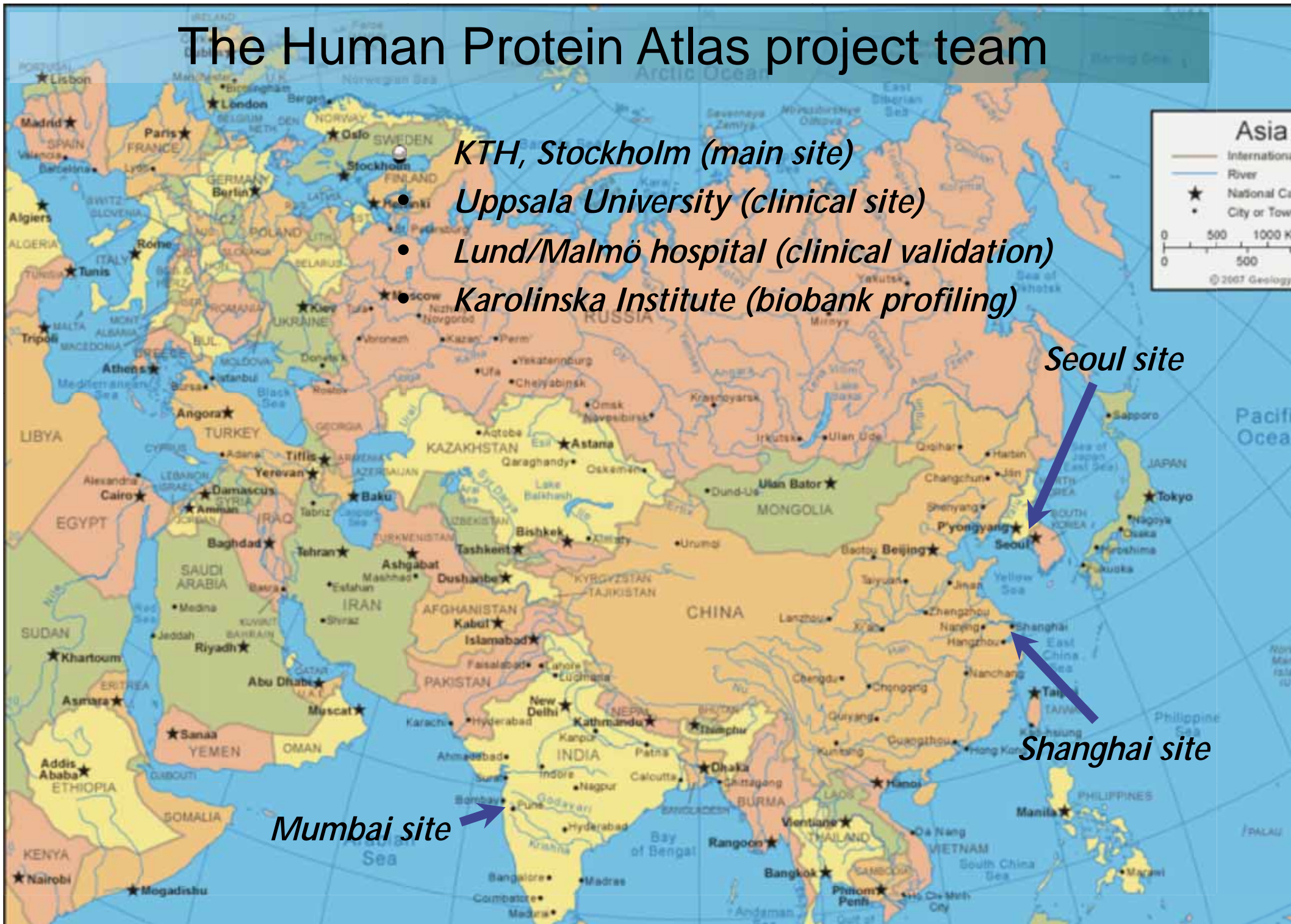
• *Lund/Malmö hospital (clinical validation)*

• *Karolinska Institute (biobank profiling)*

Seoul site

Shanghai site

Mumbai site



Mumbai

Dr. Sanjay Navani



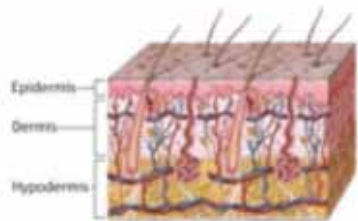
- *12 certifierade pathologist*
- *Web-based annotation*
- *Analyze 10,000 images per day*

Protein expression profiling

Protein profiling at different levels

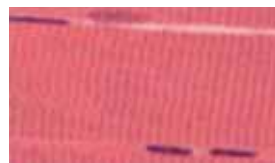


ORGANS

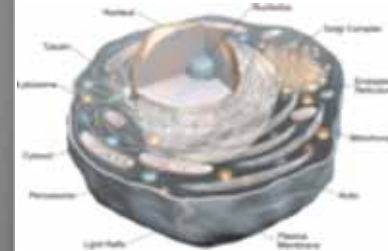


#ADAM

TISSUES

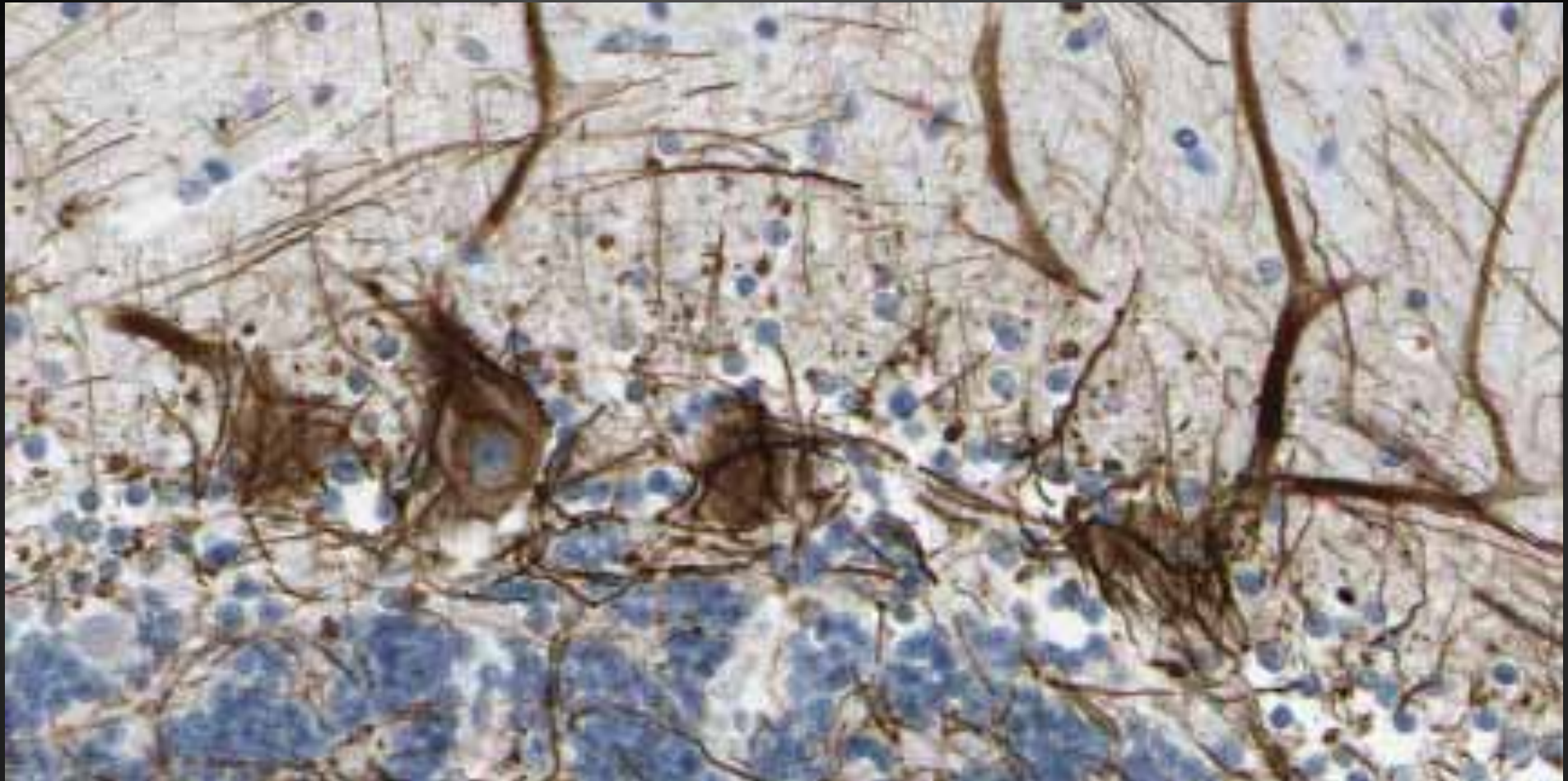


CELLS



ORGANELLES





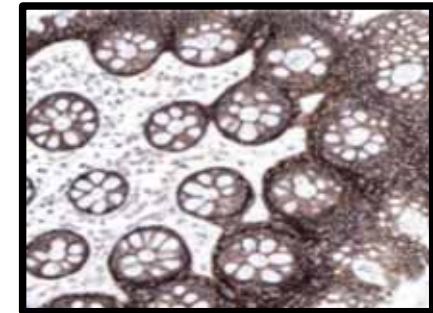
Immunohistochemical staining of human cerebellum using an antibody CAB010763 towards neurofilament, light polypeptide.

Version 7 (November 15) - more than 10 million images



Normal tissues (IHC)

- 48 organs and tissues
(including liver, kidney, GI-tract,
heart, brain, pancreas, female/male
tissues etc)



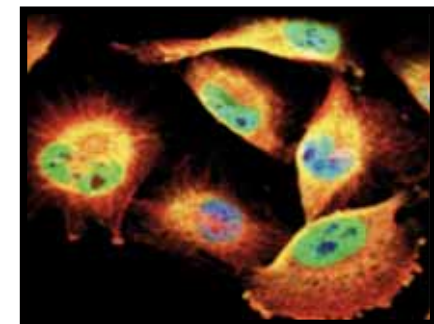
Cancer (IHC)

- 20 different types of cancer
(including breast, lung, prostate,
colon, liver, kidney etc..)



Cell lines (IF och IHC)

- 47 cell lines
- 12 clinical cell samples



50 % of all protein-coding genes



THE HUMAN PROTEIN ATLAS ABOUT & HELP

SEARCH

HYDIN Search Clear Fields »

e.g. Her2, transcribion factors, chromosome X, strong expression in prostate or click fields for options.

ABCF2 (HPA030386)
Immunohistochemical staining of human testis shows nuclear, cytoplasmic positivity in both cells in seminiferous ducts and leydig cells.

Version 7.0
11,276 antibodies and 8,101,793 images

The HPA project is funded by the Knut & Alice Wallenberg foundation. The atlas is part of the HUPO Human Antibody Initiative (HAI).

UPPSALA UNIVERSITY



10,118 genes



November 15, 2010



New design



From database to “knowledge-base”

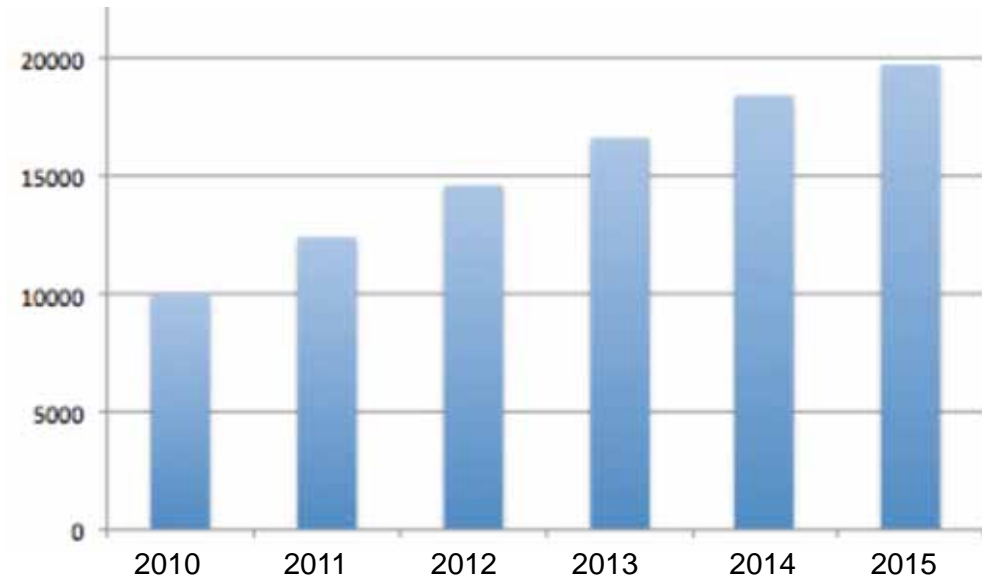


New structure



Much more information

The next five years



- *Approximately 8 new genes completed per day*
- *First draft of the human proteome by 2015 (19,700 genes)*
- *Long-term objective: paired antibodies to all human proteins*

4

Personalized medicine

Personalized medicine - two strategies



Analysis of body fluids

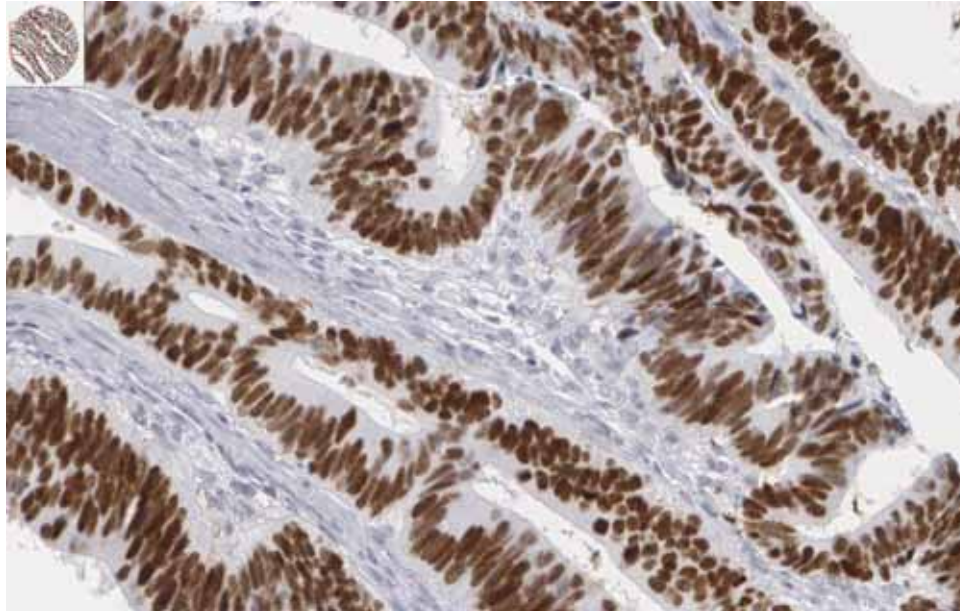
- **plasma/serum**
- **urine**
- **CSF**



Analysis of specific cells and tissues

- **biopsy (pathology)**
- **flow sorting (cells from blood)**
- **whole body imaging (PET, SPECT)**

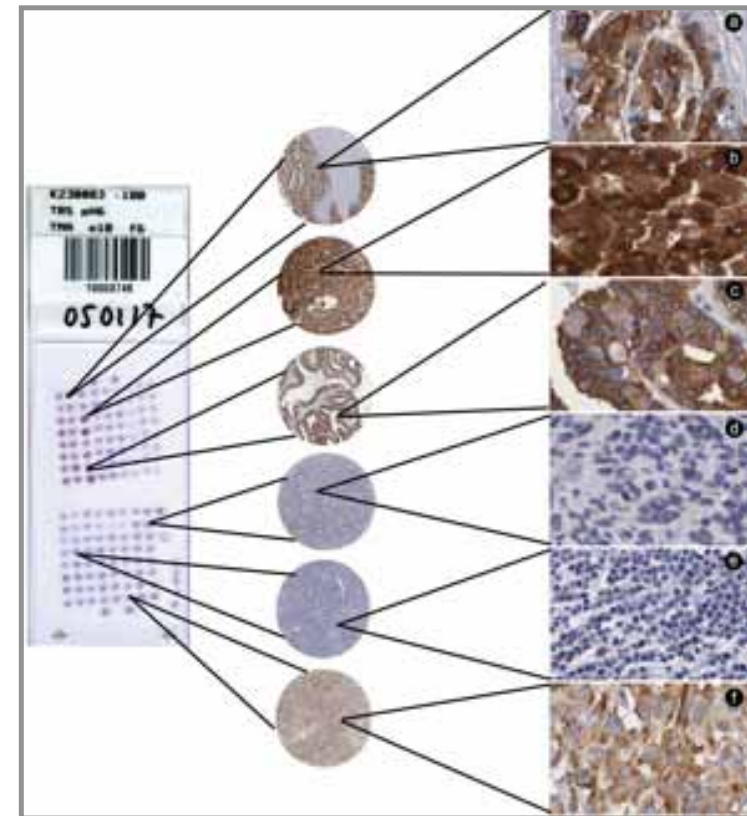
Cancer



1. Cancer börjar i en enskild cell
2. Cancer beror på skillnader i proteiner (gener)
3. Nyckelprocesser i cellen har påverkats

Cancers in the Human Protein Atlas

Cancer type	Basis for stratification	Included phenotypes	Number of subgroups
Breast cancer	Elston score and phenotype	Ductal and lobular carcinoma	4
Cervical cancer	Phenotype	Squamous cell carcinoma and adenocarcinoma	2
Colo-rectal cancer	Dukes classification	Adenocarcinoma	3
Endometrial cancer	FIGO score	Adenocarcinoma	3
Head and Neck cancer	No stratification	Squamous cell carcinoma and adenocarcinoma	1
Liver cancer	Phenotype	Hepatocellular and cholangiocellular	2
Lung cancer	Phenotype	Squamous cell carcinoma and adenocarcinoma	2
Malignant Carcinoids	No stratification	Primary and metastatic carcinoids	1
Malignant Glioma	Malignancy grade	High-grade and low-grade glioma	2
Malignant Lymphoma	Malignancy grade and	High-grade, low-grade non-Hodgkin lymphoma	3
Malignant Melanoma	Breslow (Tumor thickness)	Primary cutaneous and metastatic melanoma	4
Ovarian cancer	Phenotype	Serous, mucinous and endometrioid	3
Pancreatic cancer	No stratification	Adenocarcinoma	1
Prostate cancer	Gleason grade	Adenocarcinoma	3
Renal cancer	No stratification	Adenocarcinoma	1
Skin cancer	Phenotype	Basal and squamous cell carcinoma	2
Stomach cancer	Phenotype	Diffuse and intestinal adenocarcinoma	2
Testicular cancer	Phenotype	Seminoma and non-seminoma	2
Thyroid cancer	No stratification	Papillary and follicular carcinoma	1
Urinary bladder cancer	Malignancy grade	High-grade and low-grade Urothelial carcinoma	2



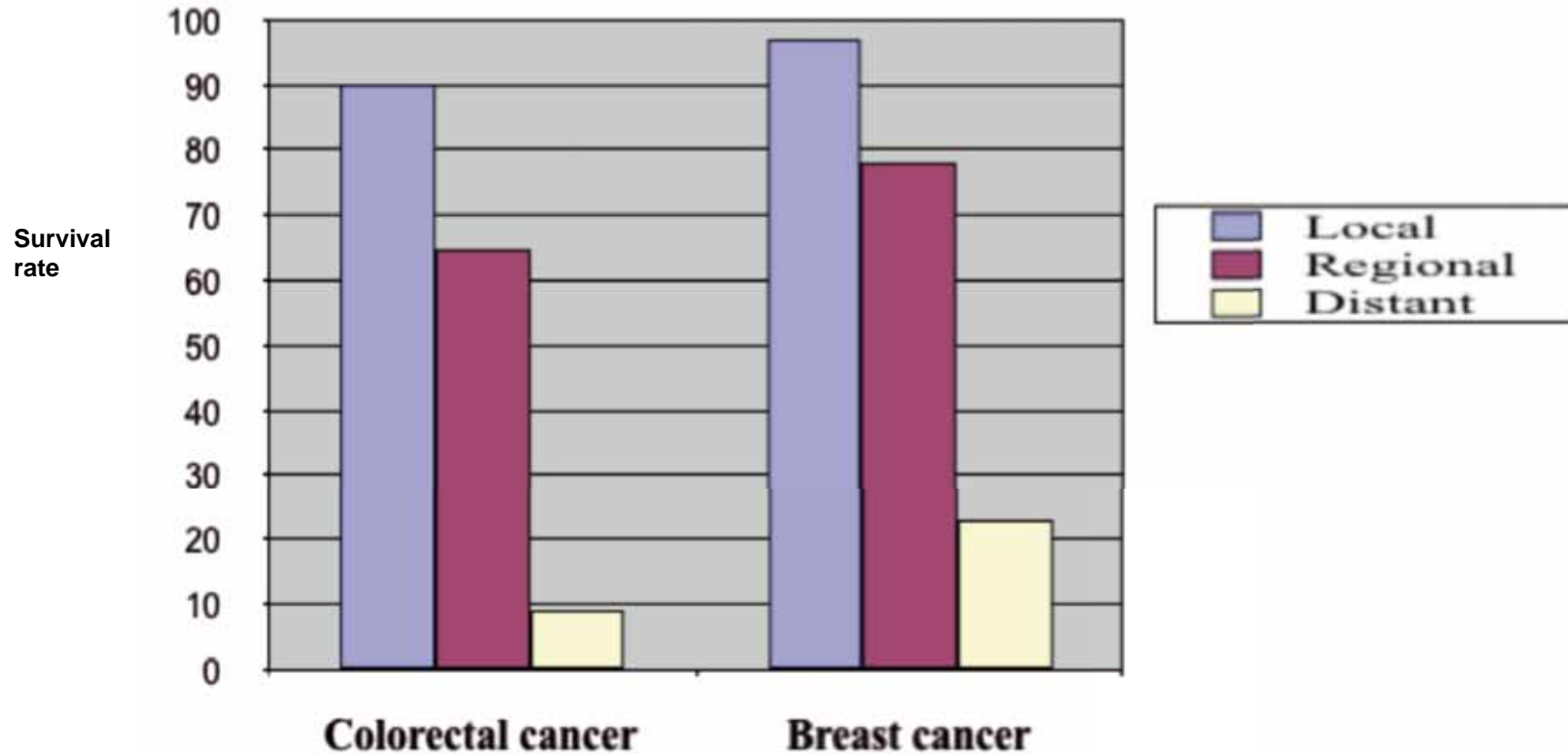
20 different types of cancer

216 patients

12 different patients of each type

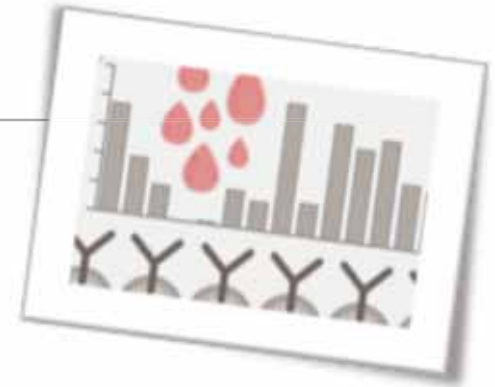
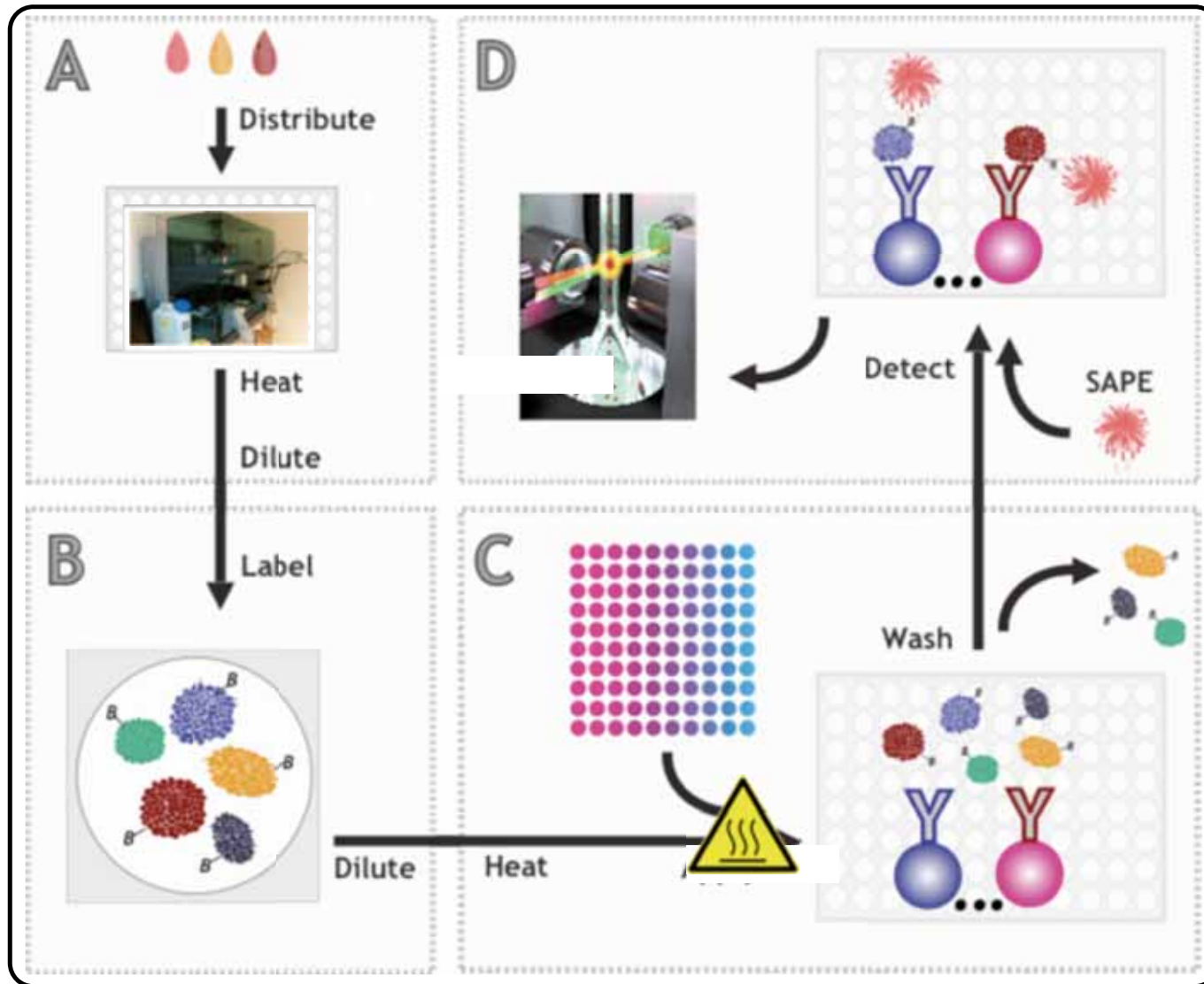
Tumors stratified according to histopathology

Tidig upptäckt av cancer oerhört viktigt



Tidig upptäckt kan ge 70-80% minskad dödlighet

High-throughput workflow



research articles **proteome** research

Antibody Suspension Bead Arrays within Serum Protocols

Isabel M. Schmitt,¹ Martin Cox, Sabrina Ghosh, Ralfine Thiele, and Peter Weiss

¹Department of Proteomics, School of Biotechnology, EPIC (European Proteomics Innovation Centre), Imperial College London, London SW7 2BZ, United Kingdom

Received November 26, 2010

150,000 assays in one run !!!

Population-based biobanks

- **120** large (> 10 000 participants)
- **1/4** of all biobank samples are found in the Nordic Countries



*Extracted from P³G
Observatory*

Collection of disease cohorts



Lung cancer
Prostate cancer
Colorectal cancer
Breast cancer
Ovarian cancer
Malignant melanoma
Pancreatic cancer
Stomach cancer
Kidney cancer
Bladder cancer
Minimal cognitive impairment
Alzheimer dementia
Parkinson
Amyotrophic lateral sclerosis
Multiple sclerosis
Instable angina
Cardiac insufficiency
Cardiac arhythmia
Venous tromembolism
Aortic aneurysm
Osteoporosis

Type of biomarkers

Diagnostic markers

- High specificity - detection of specific disease
- Blood or body fluids (early detection)
- Tissue (differential diagnostics)

Prognostic markers

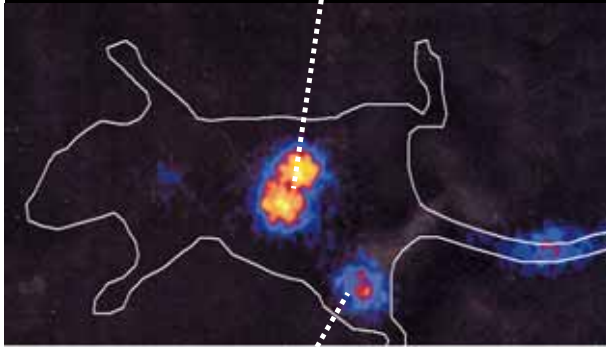
- Differential expression - correlation with patient outcome
- Stratification of high versus low risk patients
- Guide for patient information and monitoring

Predictive markers

- Differential expression - correlation with response to specific therapy
- Stratification of responders versus non-responders
- Guide to determine selection of therapeutic regime

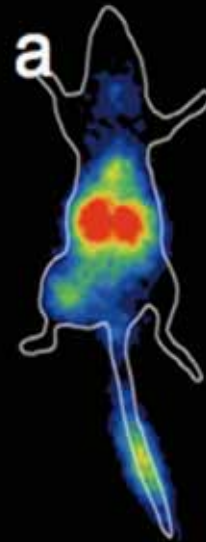
Affibodies for tumor targeting

Kidneys

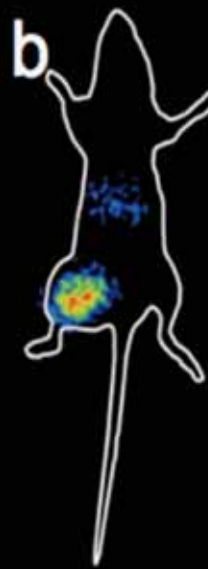


Tumor

Anti HER2-Affibody



6 hr,
50 nM
binder



6 hr,
20 pM
binder



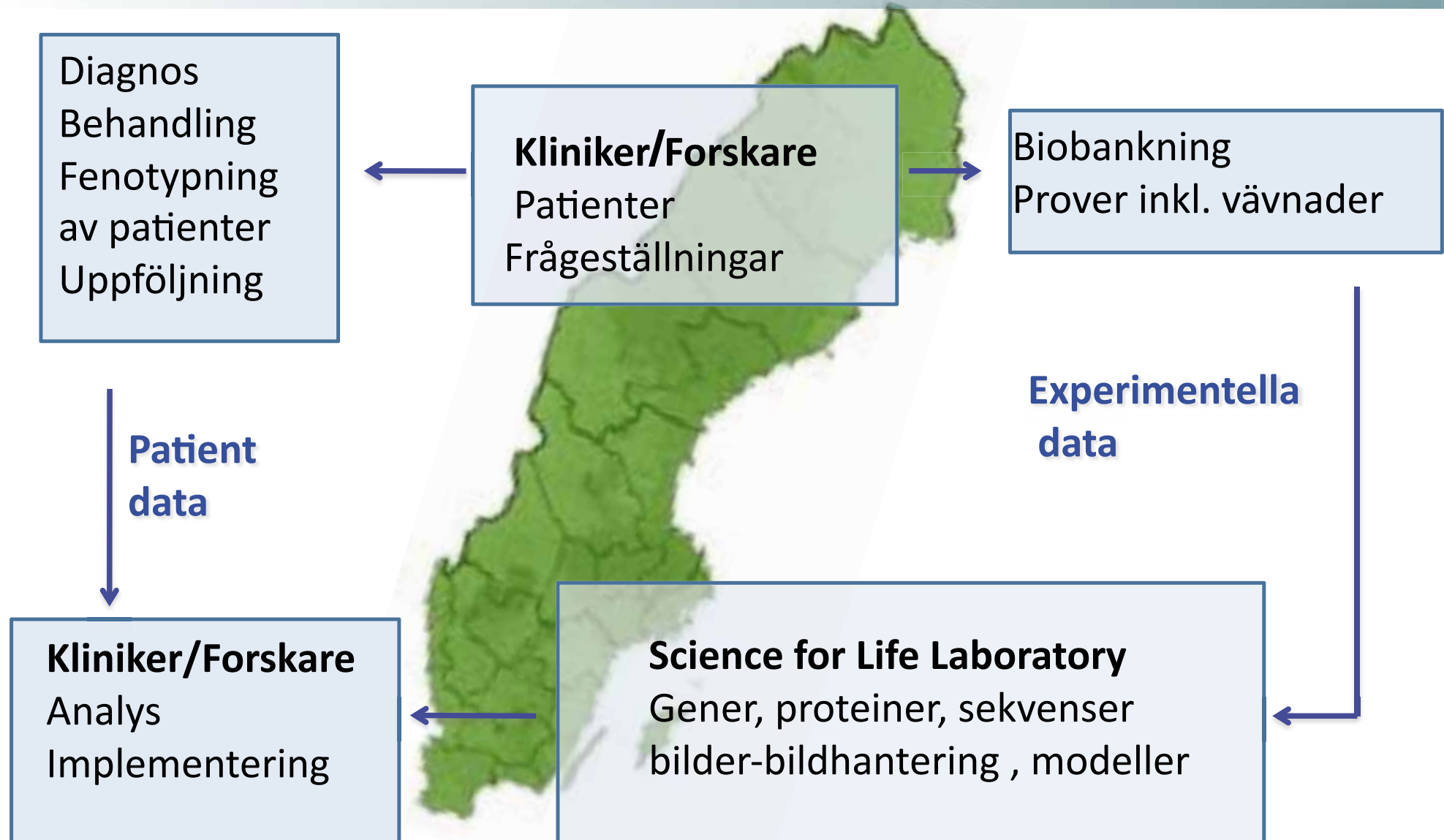
24 hr,
20 pM
binder

5

Future prospects

Human health (translational medicine)

The exploitation of molecular bioscience to develop new diagnostics and therapy and to ultimately improve the treatment of patients



Traditional drug versus individualized therapy

Traditional pharmaceutical drug

- An average drug to an average patient
- Find optimal dose with good efficacy without serious side-effects

Individualized drug treatment

- An individual treatment to an individual patient
- Stratify patients into responders and non-responders
- Develop diagnostic test for choice of treatment (or dose)
- Avoid treatment of patients which will have serious side-effects

The Swedish Protein Atlas Team (2010)



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- Henrik Wernerus
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Thanks for your attention !

