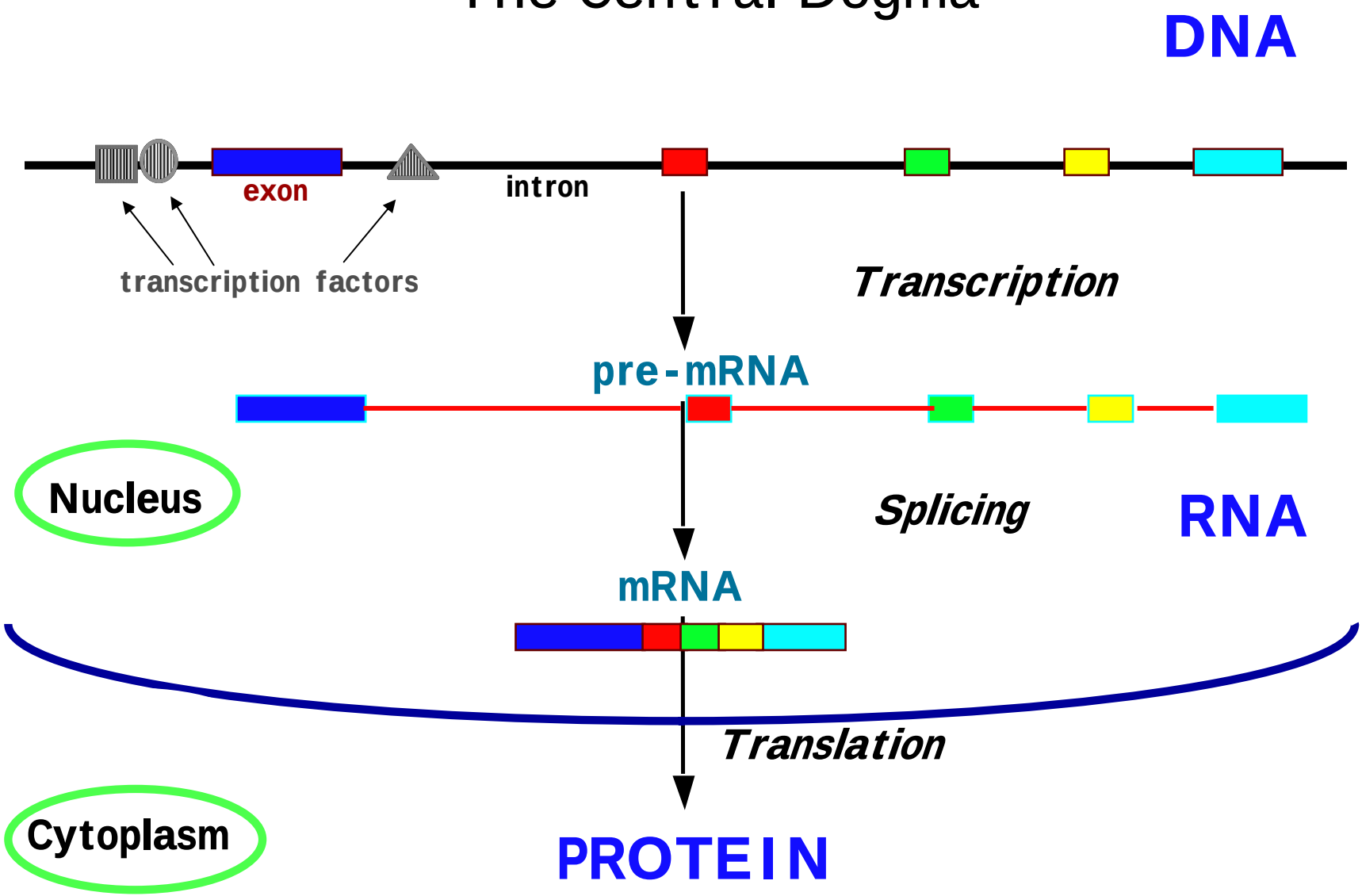
Genomics and "-omics". Applications for health

Brandon Wainwright

Institute for Molecular Bioscience
University of Queensland

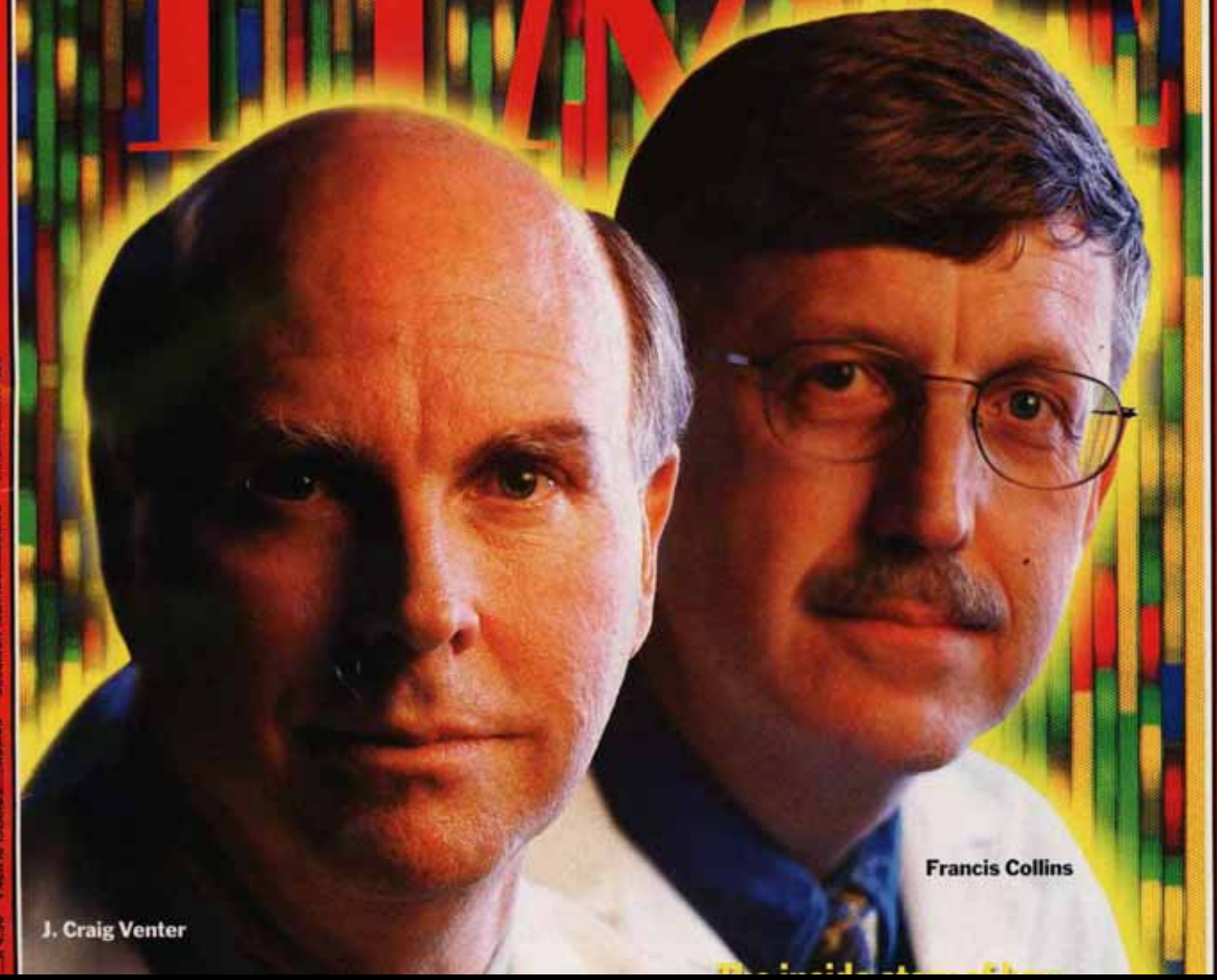
The Central Dogma



- OMICS - the “industrialisation” of molecular biology/genetics

JULY 3, 2000 $3.95 (PRE-GST) $4.30 (INCL. GST)

TIME



J. Craig Venter

Francis Collins

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- **January 23:** Celera Genomics Reports Second Quarter Fiscal 2003 Results [more...]

  additional: Applera Corporation Teleconference January 23, 2003 Management Remarks for Second Quarter Fiscal 2003 Earnings Call [more...]
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articles

Functional annotation of a full-length mouse cDNA collection

The RIKEN Genome Exploration Research Group Phase II Team and the FANTOM Consortium*

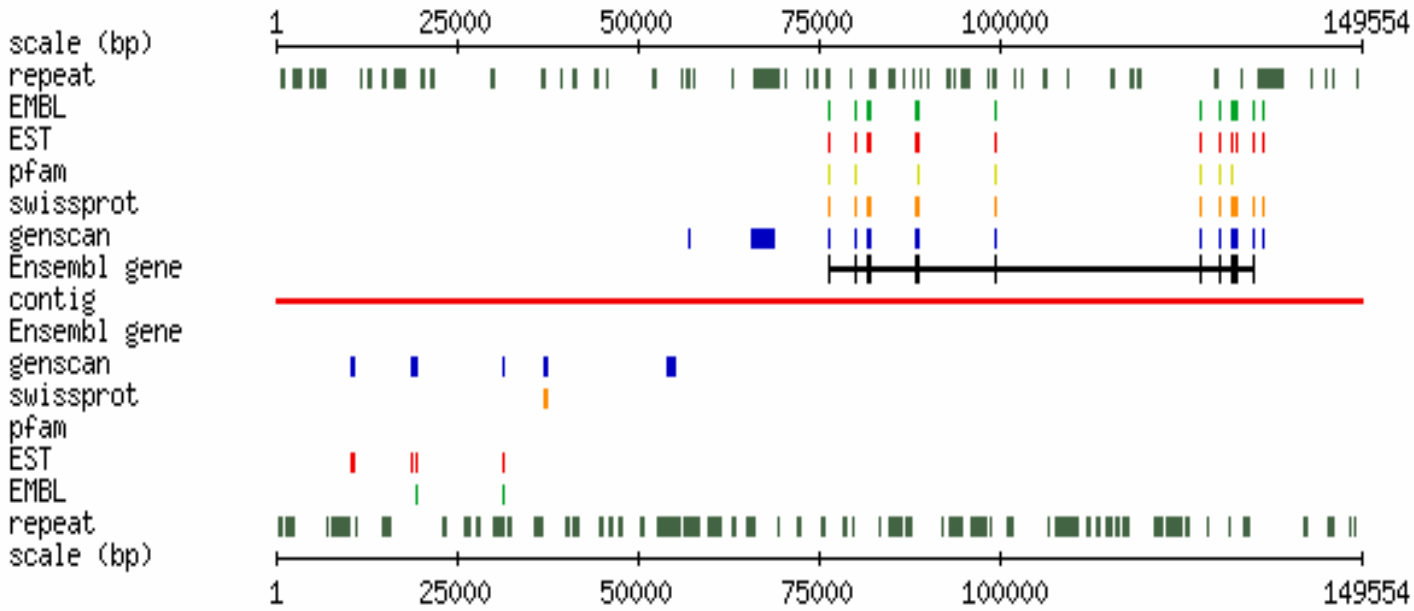
The RIKEN Mouse Gene Encyclopaedia Project, a systematic approach to determining the full coding potential of the mouse genome, involves collection and sequencing of full-length complementary DNAs and physical mapping of the corresponding genes to the mouse genome. We organized an international functional annotation meeting (FANTOM) to annotate the first 21,076 cDNAs to be analysed in this project. Here we describe the first RIKEN clone collection, which is one of the largest described for any organism. Analysis of these cDNAs extends known gene families and identifies new ones.

Nature 409, 685-690,2001

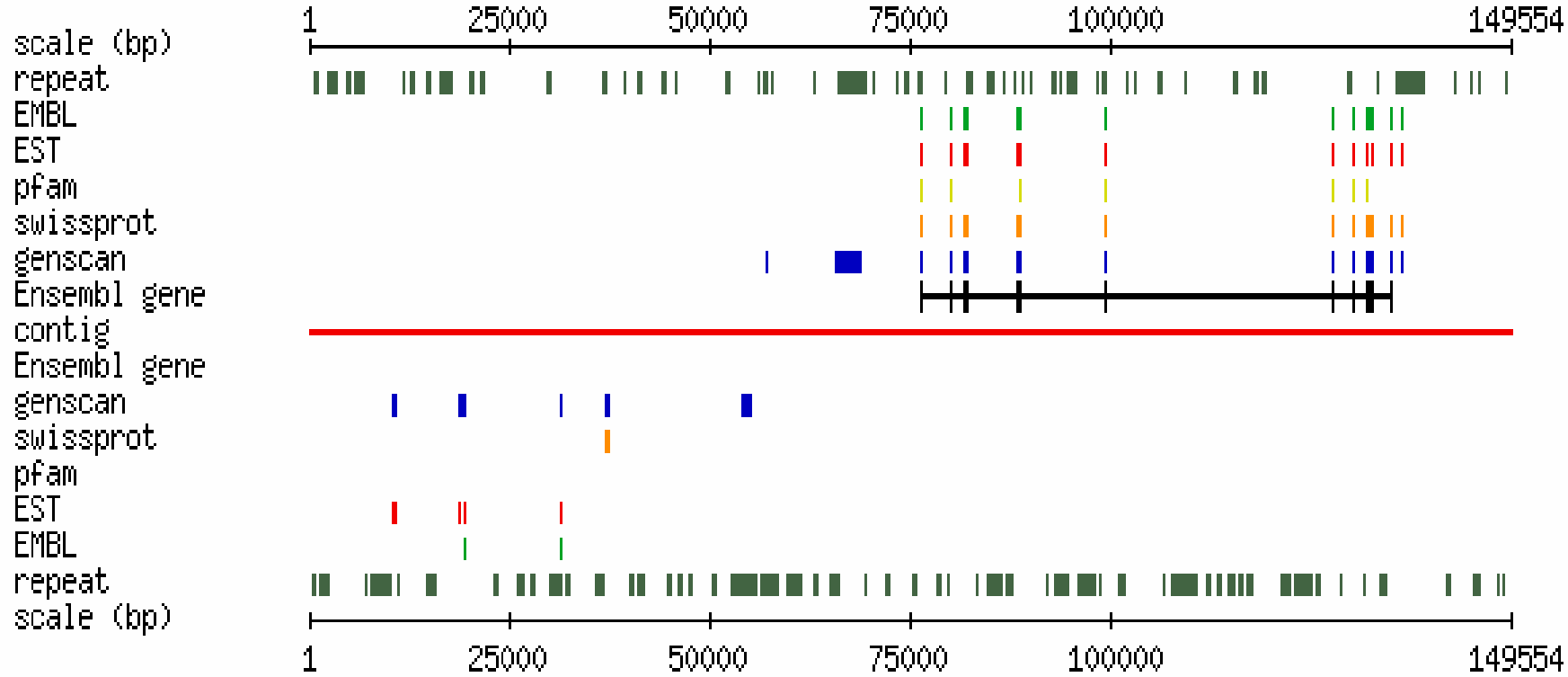
Sequence AC000111 has 1 contig(s)

This Ensembl entry has been reannotated from an orginal EMBL source file
View this Ensembl sequence annotated in [EMBL | GenBank] flat file format
Click a gene in any graphical contig display below to access detailed gene information

Contig AC000111.00001:



Contig AC000111.00001:



View this Ensembl sequence annotated in [EMBL | GenBank] flat file format

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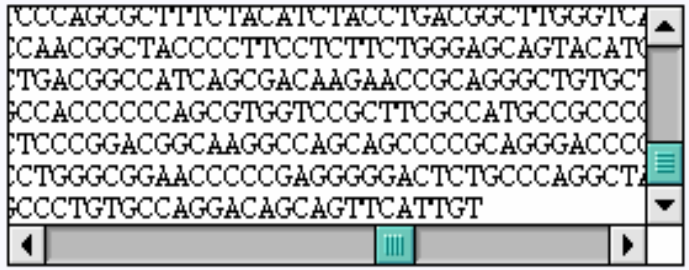
[Announcements]

Paste your DNA or protein sequence here. FASTA format or plain text will do.

Search Reset



OR select the sequence file you wish to search

Browse...

RESULTS

Browser **OR** Email to

OPTIONS

Database: Ensembl total DNA

Executable: BLASTN (DNA vs. DNA)

Report 100 alignments.

- [x] Mask repetitive sequences using Repeatmasker.
- [x] Filter low complexity regions.
- [ ] Display histogram of score statistics.

ADVANCED OPTIONS [Help]

Matrix: blosum62

Expect (E): 10

```
Reference:  Gish, Warren (1994-1997).  unpublished.
Altschul, Stephen F., Warren Gish, Webb Miller, Eugene W. Myers, and David J.
Lipman (1990).  Basic local alignment search tool.  J. Mol. Biol. 215:403-10.

Notice:  this program and its default parameter settings are optimized to find
nearly identical sequences rapidly.  To identify weak similarities encoded in
nucleic acid, use BLASTX, TBLASTN or TBLASTX.

Query=  UNKNOWN-QUERY
        (3024 letters)

Database: ensembl.dna.fa
          378,909 sequences; 3,083,927,556 total letters.
Searching....10....20....30....40....50....60....70....80....90....100% done
```

Sequences producing High-scoring Segment Pairs:	High Score	Smallest Sum Probability P(N)	N
AC027096.00019	2727	0.0	7
AL161729.00253	2056	7.4e-257	6
AL161729.00382	2723	3.1e-142	2
AL161729.01216	1300	7.4e-67	2
AL161729.00511	731	2.5e-48	2
AL136380.00511	655	9.9e-31	2
AL161729.00518	510	4.3e-17	2
AP001625.00001	265	0.40	1
AL121673.05550	251	0.89	1
AL117379.03522	251	0.89	1
AL135910.01169	249	0.93	1

```
>AC027096.00019  [Full Sequence]              Length = 27,448

  Minus Strand HSPs:

 Score = 2727 (409.2 bits), Expect = 0.0, Sum P(7) = 0.0
```

nature genetics

volume 25 no. 2 pp 239 - 240

JUNE 2000

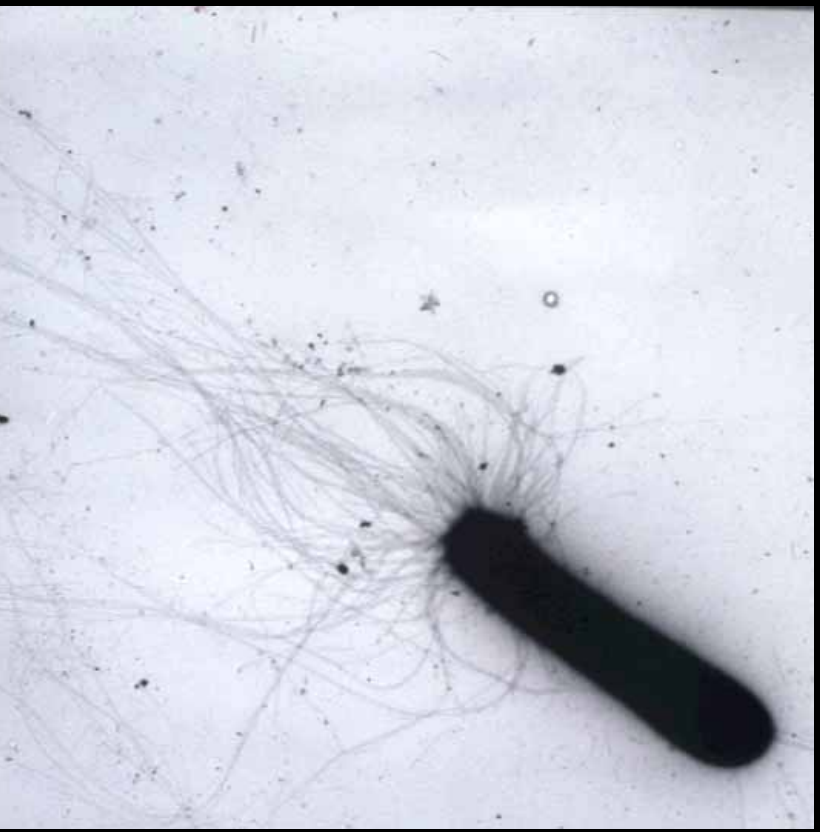
Gene Index analysis of the human genome estimates approximately 120,000 genes

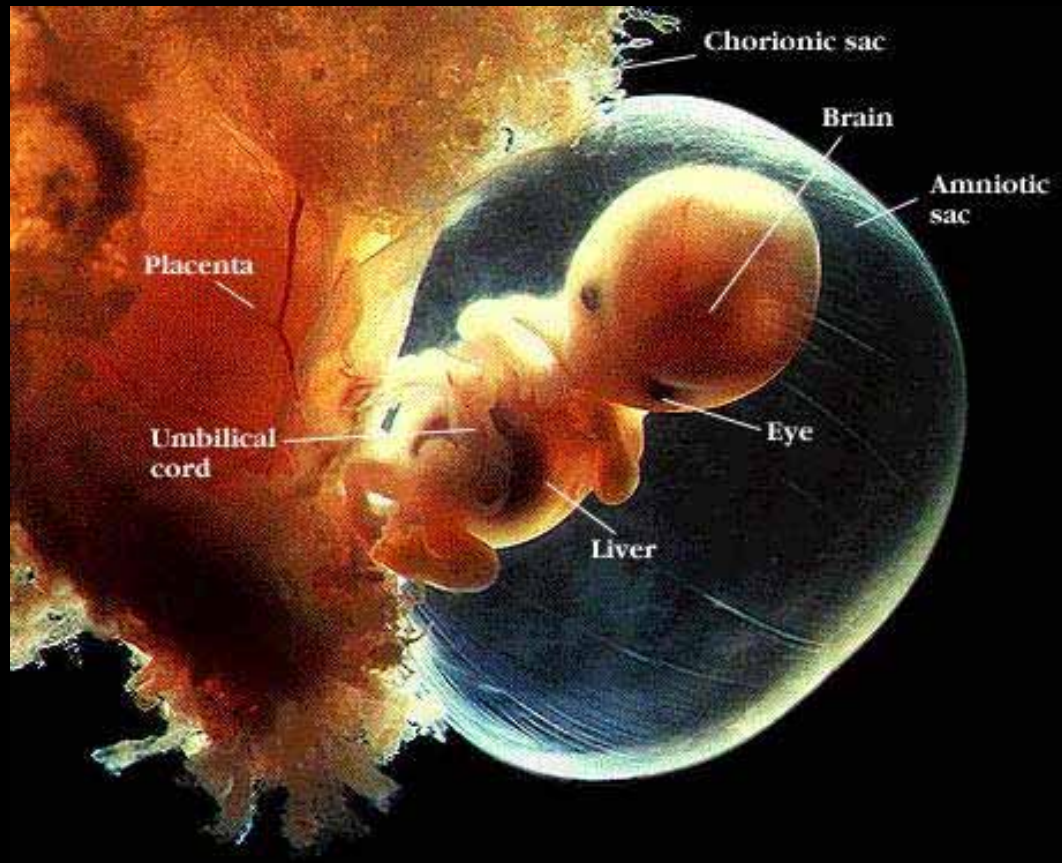
Feng Liang, Ingeborg Holt, Geo Pertea, Svetlana Karamycheva, Steven L. Salzberg & John Quackenbush

The Institute for Genomic Research, Rockville, Maryland, USA.
Correspondence should be addressed to J Quackenbush. e-mail: johnq@tigr.org

Although sequencing of the human genome will soon be completed, gene identification and annotation remains a challenge. Early estimates suggested that there might be 60,000–100,000 (ref. 1) human genes, but recent analyses of the available data from EST sequencing projects have estimated as few as 45,000 (ref. 2) or as many as 140,000 (ref. 3) distinct genes. The Chromosome 22 Sequencing Consortium estimated a minimum of 45,000 genes based on their annotation of the complete chromosome, although their data suggests there may be additional genes[4]. The nearly 2,000,000 human ESTs in dbEST provide an important resource for gene identification and genome annotation, but these single-pass sequences must be carefully analysed to remove contaminating sequences, including those from genomic DNA, spurious transcription, and vector and bacterial sequences

The problem of development

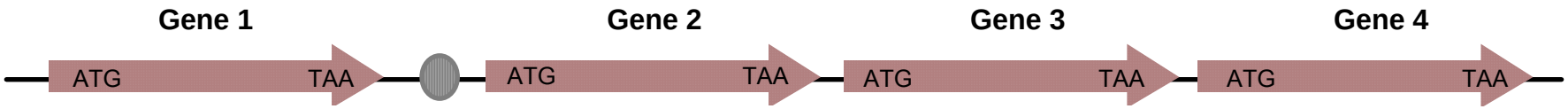


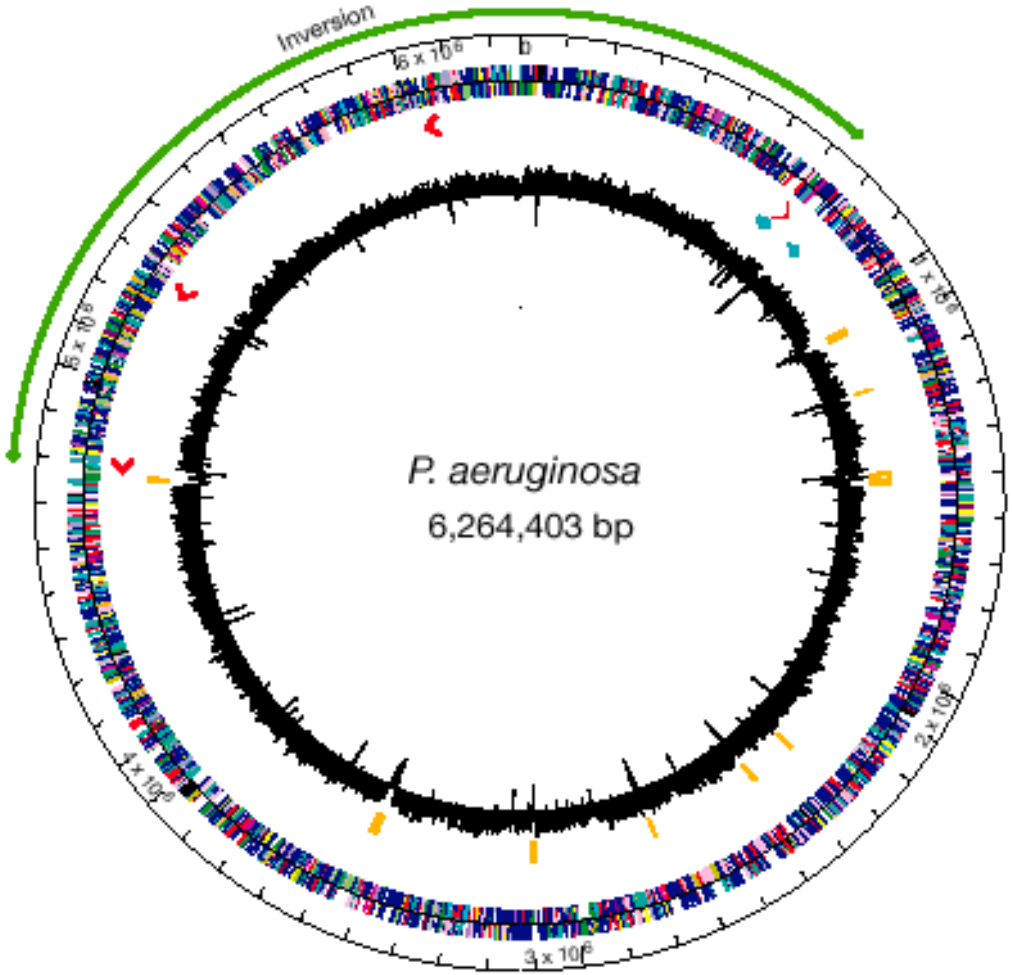


Unicellular > colonial, limited differentiation

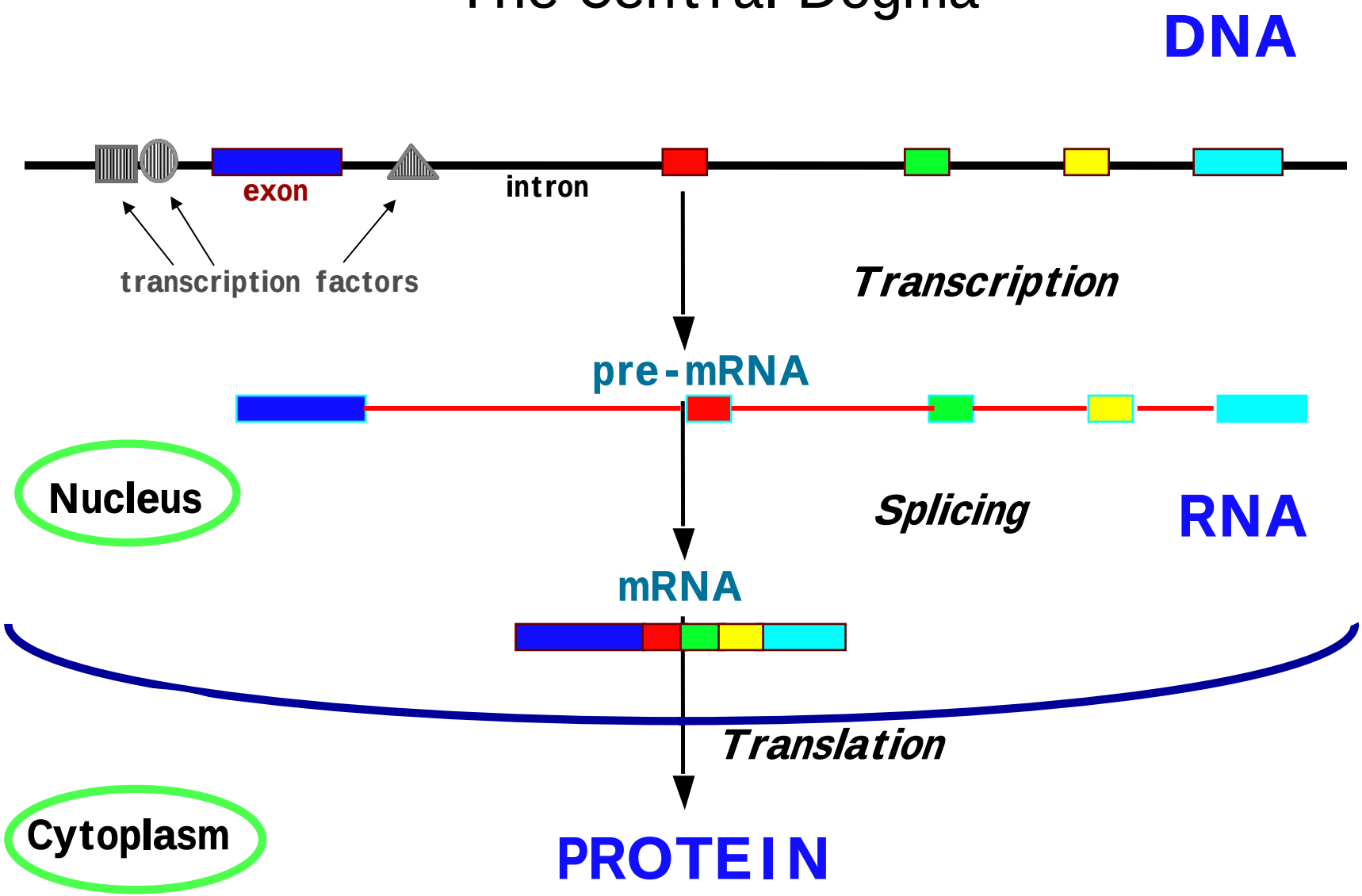
~10^{14} positionally distinct cells, with precise architecture and differentiated function

Central dogma and the lac paradigm: genes are synonymous with proteins





The Central Dogma



Non-coding RNA?
Micro RNA?

The genetic basis of eukaryotic complexity and variation

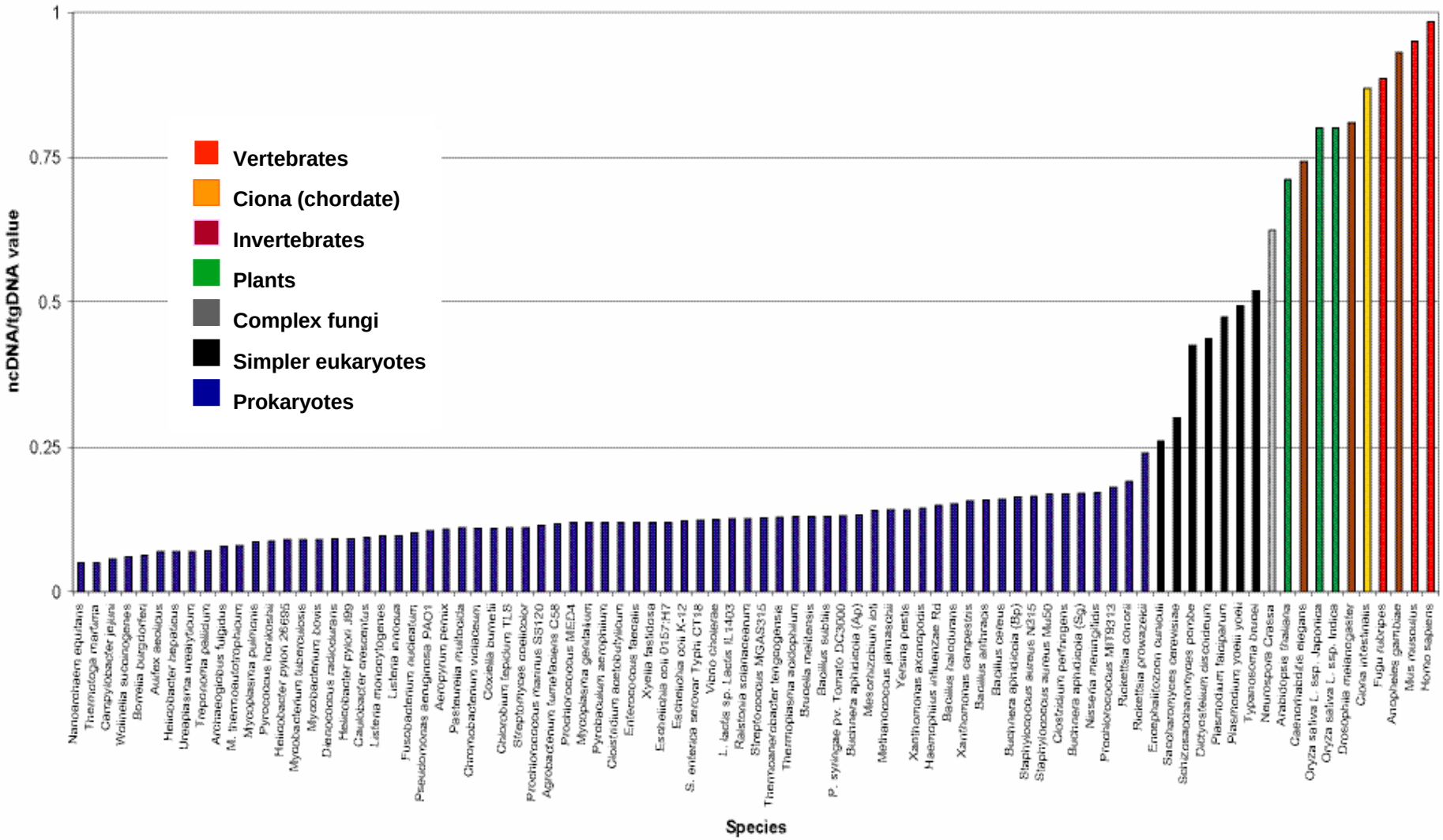
- The number of protein-coding genes does not scale strongly or consistently with complexity: Just 5% of our genome

  - insects only have just over twice as many protein-coding genes (~13,500) as yeast (~6,000) and *P. aeruginosa* (~5,200).

  - insects have 50% fewer protein-coding genes than the nematode worm *C. elegans* (~19,000), which has only 1,000 cells.

  - vertebrate (human, mouse, fish) protein-coding gene numbers (30,000) are only slightly higher than that of *C. elegans*, and less than those of plants (rice ~40,000).

- The relative amount of noncoding DNA does scale with complexity.



R.J. Taft and J.S. Mattick, http://genomebiology.com/2003/5/1/P1

3 MAY 2002 VOL 296 SCIENCE

Large-Scale Transcriptional Activity in Chromosomes 21 and 22

Philipp Kapranov,[1] Simon E. Cawley,[1] Jorg Drenkow,[1] Stefan Bekiranov,[1] Robert L. Strausberg,[2] Stephen P. A. Fodor,[1] Thomas R. Gingeras[1]*

The sequences of the human chromosomes 21 and 22 indicate that there are approximately 770 well-characterized and predicted genes. In this study, empirically derived maps identifying active areas of RNA transcription on these chromosomes have been constructed with the use of cytosolic polyadenylated RNA obtained from 11 human cell lines. Oligonucleotide arrays containing probes spaced on average every 35 base pairs along these chromosomes were used. When compared with the sequence annotations available for these chromosomes, it is noted that as much as an order of magnitude more of the genomic sequence is transcribed than accounted for by the predicted and characterized exons.

Cell, Vol. 116, 499–509, February 20, 2004, Copyright ©2004 by Cell Press

Unbiased Mapping of Transcription Factor Binding Sites along Human Chromosomes 21 and 22 Points to Widespread Regulation of Noncoding RNAs

Simon Cawley,[1,5] Stefan Bekiranov,[1,5] Huck H. Ng,[2,3,4] Philipp Kapranov,[1] Edward A. Sekinger,[2] Dione Kampa,[1] Antonio Piccolboni,[1] Victor Sementchenko,[1] Jill Cheng,[1] Alan J. Williams,[1] Raymond Wheeler,[1] Brant Wong,[1] Jorg Drenkow,[1] Mark Yamanaka,[1] Sandeep Patel,[1] Shane Brubaker,[1] Hari Tammana,[1] Gregg Helt,[1] Kevin Struhl,[2,*] and Thomas R. Gingeras[1,*]

[1]Affymetrix
3380 Central Expressway
Santa Clara, California 95051

[2]Deptartment of Biological Chemistry and Molecular Pharmacology
Harvard Medical School
Boston, Massachusetts 02115

[3]Department of Biological Sciences
National University of Singapore
Singapore 117543

[4]Genome Institute of Singapore
Singapore 138672

Summary

Using high-density oligonucleotide arrays representing essentially all nonrepetitive sequences on human chromosomes 21 and 22, we map the binding sites in vivo for three DNA binding transcription factors, Sp1, cMyc, and p53, in an unbiased manner. This mapping reveals an unexpectedly large number of transcription factor binding site (TFBS) regions, with a minimal estimate of 12,000 for Sp1, 25,000 for cMyc, and 1600 for p53 when extrapolated to the full genome. Only 22% of these TFBS regions are located at the 5′ termini of protein-coding genes while 36% lie within or immediately 3′ to well-characterized genes and are significantly correlated with noncoding RNAs. A significant number of these noncoding RNAs are regulated in response to retinoic acid, and overlapping pairs of protein-coding and noncoding RNAs are often coregulated. Thus, the human genome contains roughly comparable numbers of protein-coding and noncoding genes that are bound by common transcription factors and regulated by common environmental signals.

The Dog Genome: Survey Sequencing and Comparative Analysis

Ewen F. Kirkness,[1] Vineet Bafna,[2*] Aaron L. Halpern,[2*] Samuel Levy,[2*] Karin Remington,[2*] Douglas B. Rusch,[2*] Arthur L. Delcher,[1] Mihai Pop,[1] Wei Wang,[1] Claire M. Fraser,[1] J. Craig Venter[2]

Table 1. Coverage of hu…nents with dog and mouse genomic sequence. Nonre…by the best dog and mouse alignments and three-way…nbl release 11.31.1. Values represent the total length…e percentage of each class covered.

Sequence class	Dog best hits		Mouse best hits		COBs	
	Mb	%	Mb	%	Mb	%
5′-UTR	3.10	41.9	3.82	51.6	1.97	26.6
3′-UTR	10.60	52.2	10.51	50.9	5.66	27.5
CDS	20.58	60.7	26.00	76.6	17.08	50.4
Intron	192.93	26.0	109.91	14.8	46.53	6.8
Upstream (5 kb)	30.29	22.2	22.43	16.4	9.33	6.8
Downstream (5 kb)	35.04	25.9	26.27	19.4	11.75	8.7
Intergenic	360.47	18.3	179.13	9.1	77.05	3.9

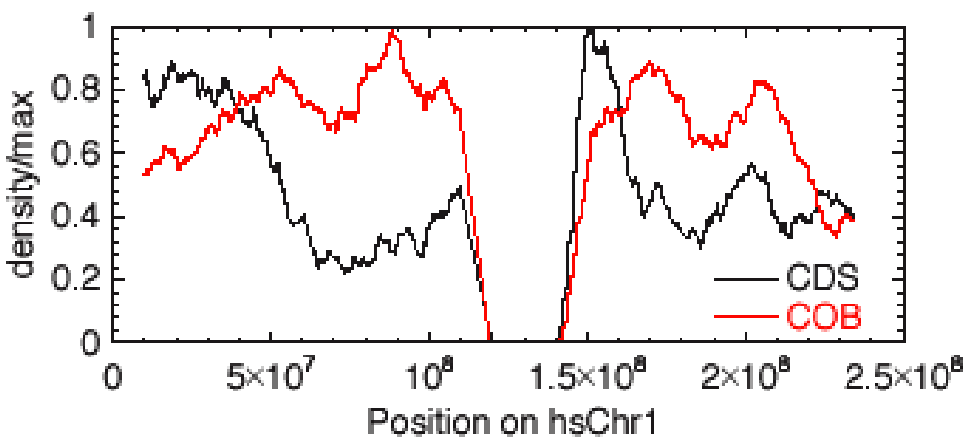


Fig. 2. The densities of COBs (red) and coding sequence (black) along human chromosome 1. They were computed as number of bases in sliding windows of 20 Mb and were normalized to the single largest value for each category.

Published online 6 May 2004
[DOI: 10.1126/science.1098119]

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Submitted on March 19, 2004
Accepted on April 27, 2004

Ultraconserved Elements in the Human Genome

Gill Bejerano [1*], Michael Pheasant [2], Igor Makunin [2], Stuart Stephen [2], W. James Kent [1], John S. Mattick [2], David Haussler [3*]

[1] Department of Biomolecular Engineering, University of California Santa Cruz, Santa Cruz, CA 95064, USA.
[2] ARC Special Research Centre for Functional and Applied Genomics, Institute for Molecular Bioscience, University of Queensland, Brisbane, QLD 4072, Australia.
[3] Howard Hughes Medical Institute, University of California Santa Cruz, Santa Cruz, CA 95064, USA.

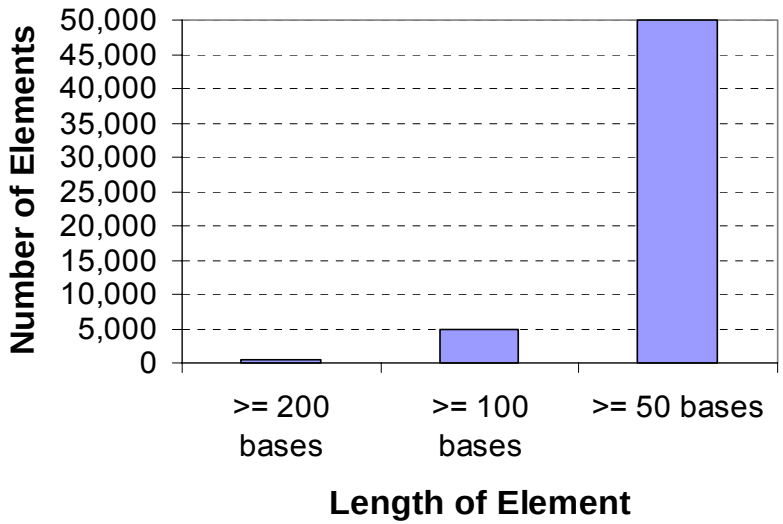
[*] To whom correspondence should be addressed.
Gill Bejerano , E-mail: jill@soe.ucsc.edu
David Haussler , E-mail: haussler@soe.ucsc.edu

There are 481 segments longer than 200 bp that are absolutely conserved (100% identity with no insertions or deletions) between orthologous regions o
Nearly all of these segments are also conserved in the chicken and dog genomes, with an average of 95% and 99% identity, respectively. Many are also
ultraconserved elements of the human genome are most often located either overlapping exons in genes involved in RNA processing or in introns or nea
transcription and development. Along with more than 5,000 sequences of over 100bp that are absolutely conserved among the three sequenced mamm
elements whose functions and evolutionary origins are yet to be determined, but which are more highly conserved between these species than proteins, a
ontogeny of mammals and other vertebrates.

Ultra-conserved (UC) elements: sequences "frozen" in vertebrates

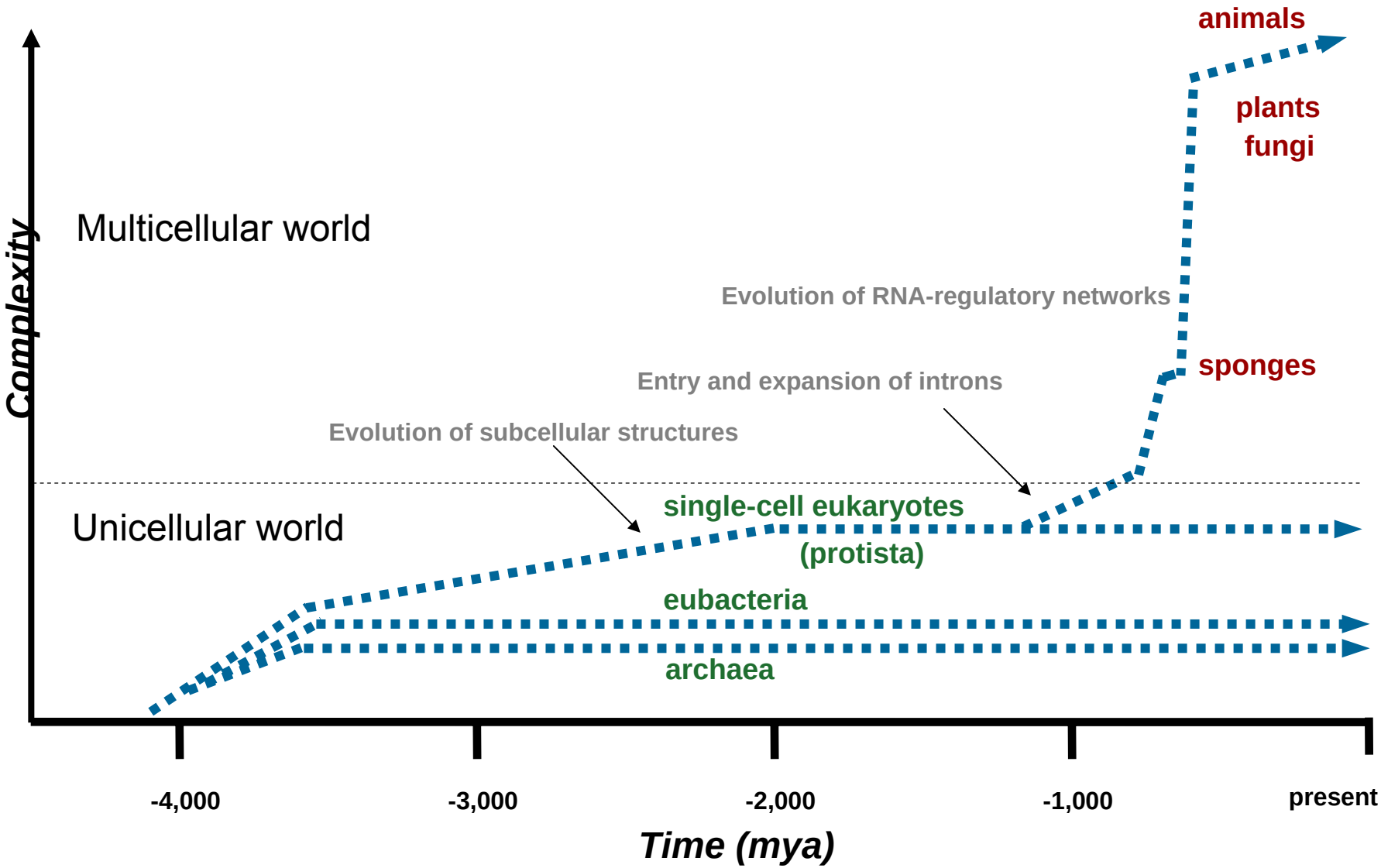
Elements	Length
481	≥ 200 n.t.
> 5,000	≥ 100 n.t.
> 50,000	≥ 50 n.t.

human-mouse-rat

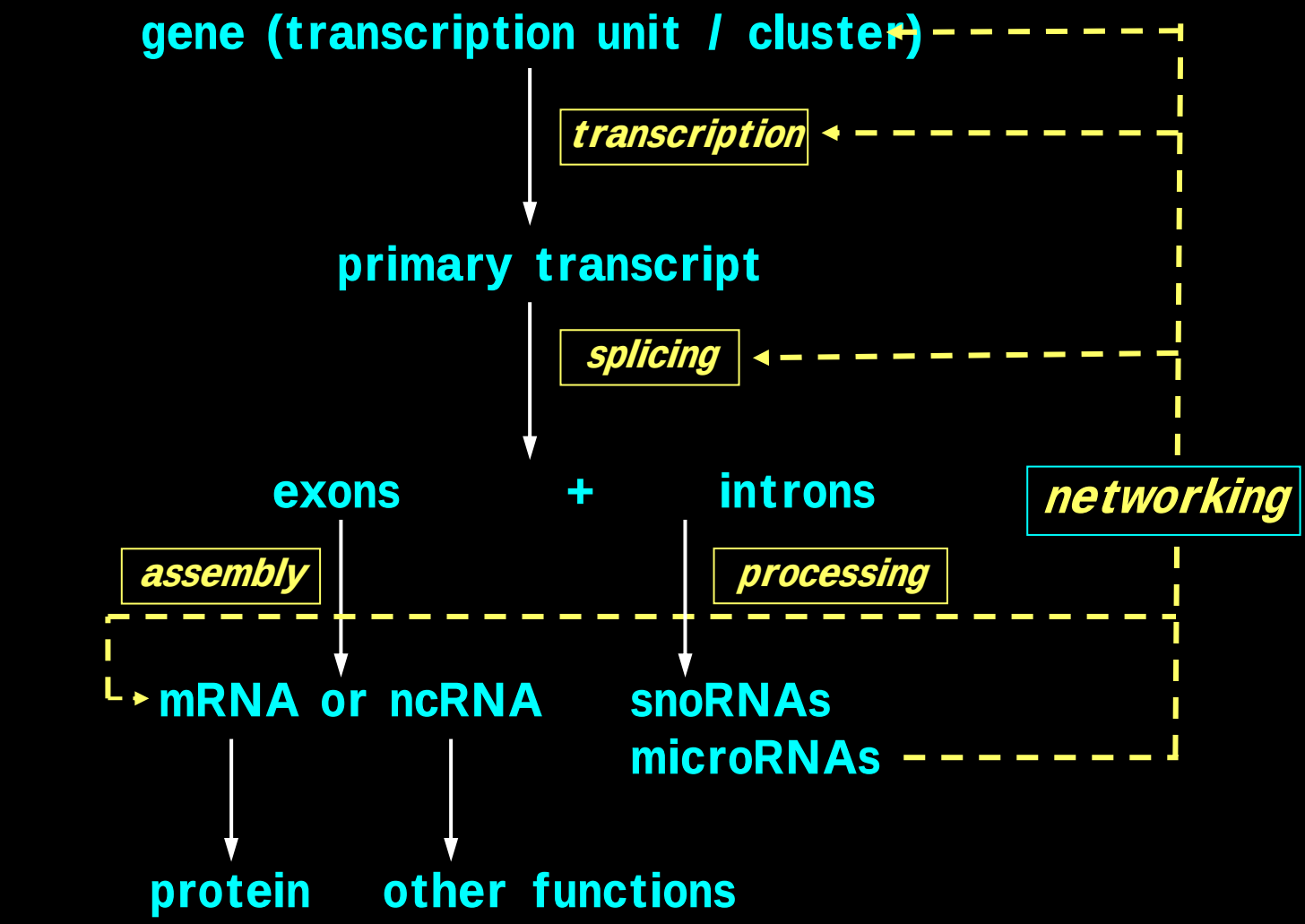


- Many more, and larger, when allow small substitutions and indels.
- All are intergenic or intronic (some overlap alternative splice sites).
- Far more conserved than protein-coding sequences. Very low probability of finding even one ultraconserved sequence by chance ($< 10^{-22}$)
- Most are conserved in chickens, two-thirds (core) conserved in fishes. Most are conserved > 400 Mya

A simplified biological history of the Earth

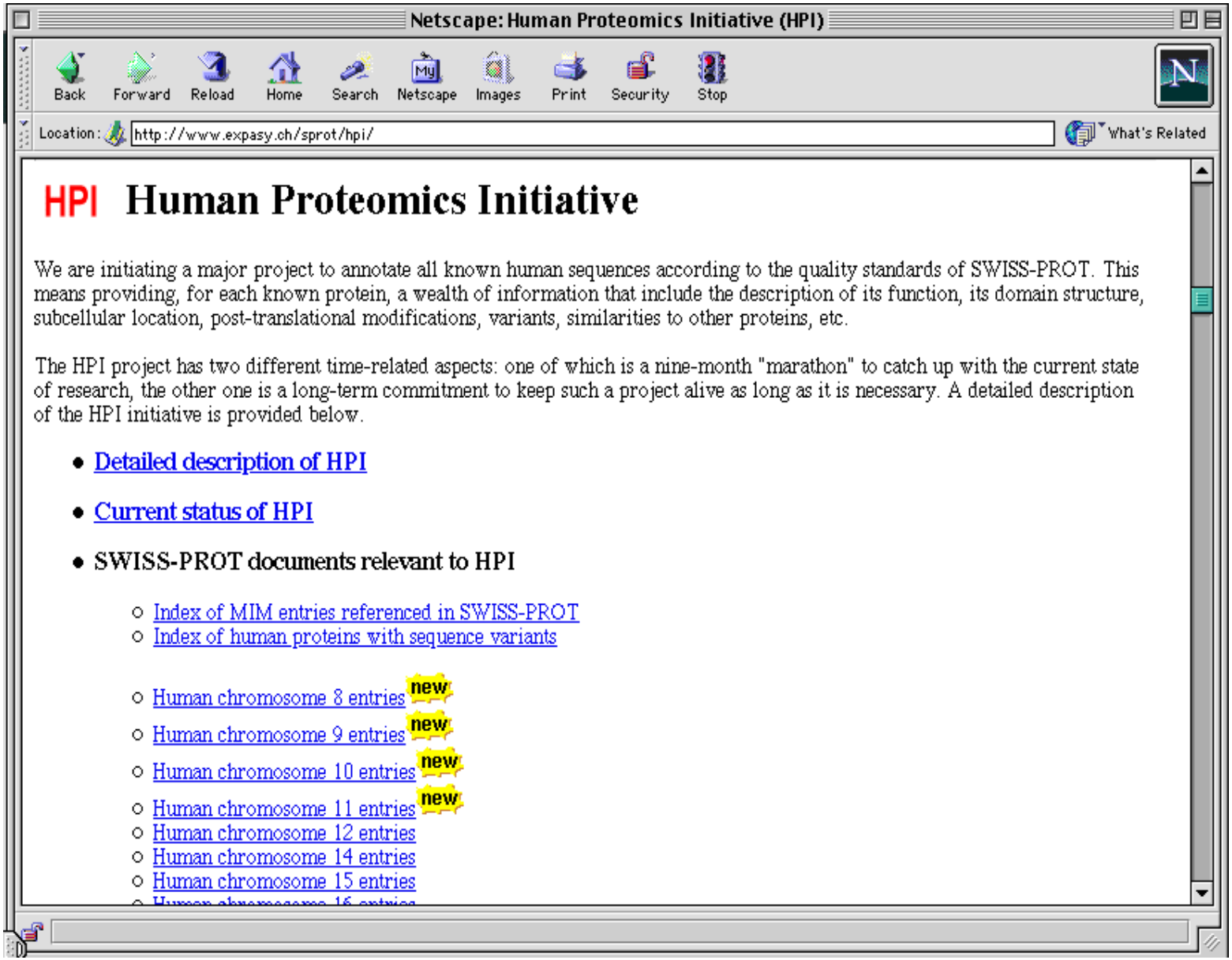


Revised definition of gene and flow of genetic information

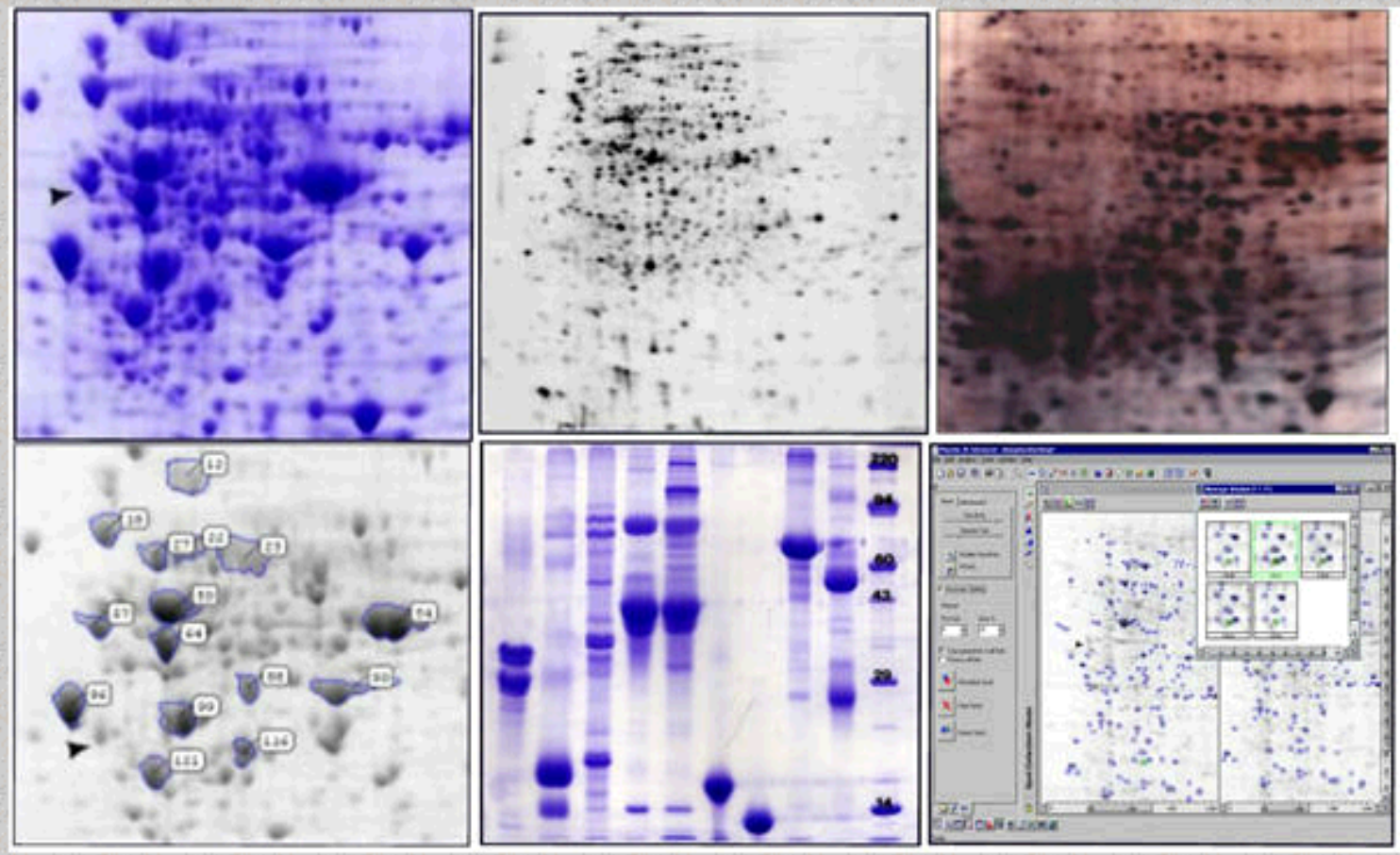


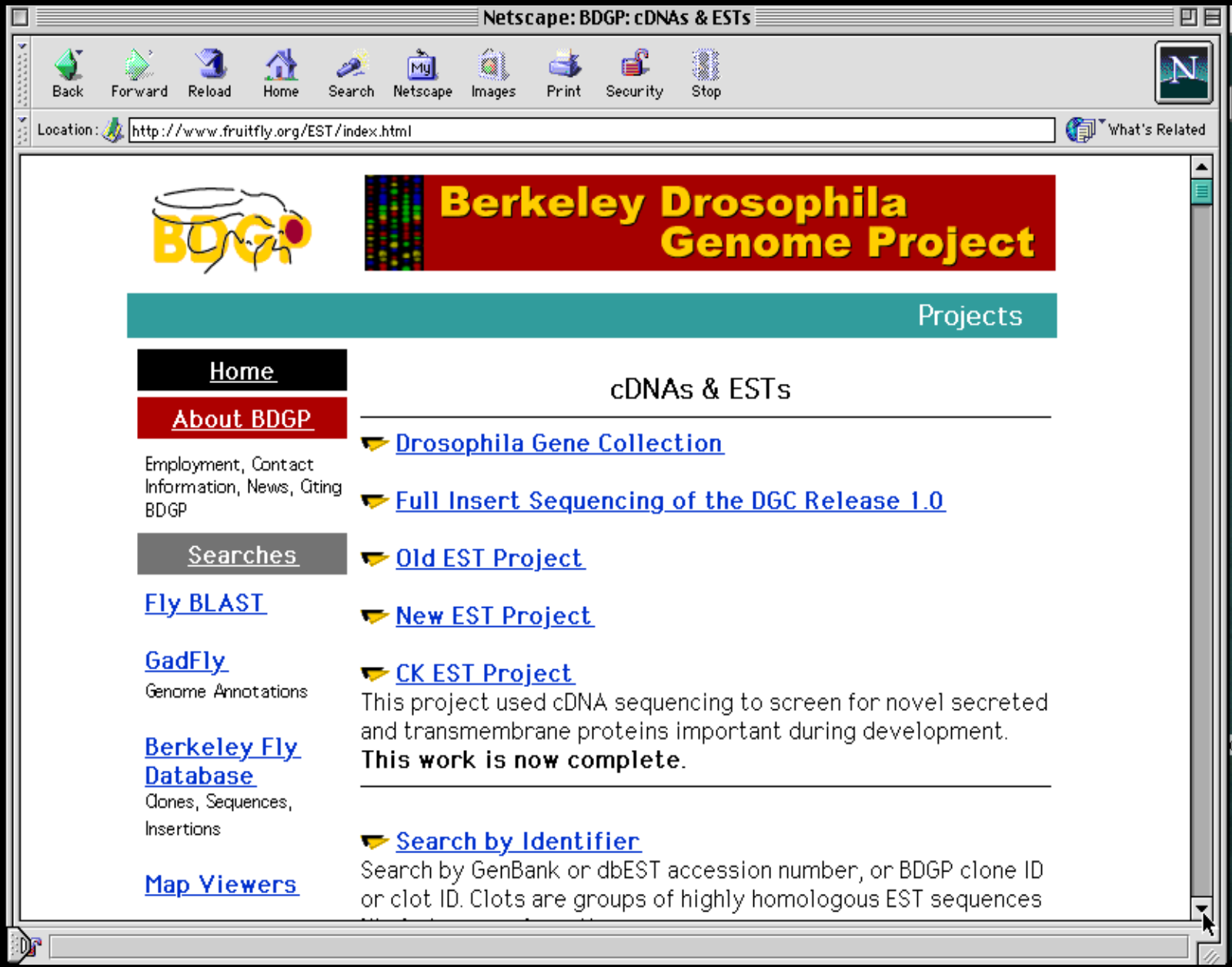
Information derived from Genomics Programs

- gene discovery (expressed sequences)
- genome variation (SNPs/polymorphisms)
- genome architecture (transposable elements/evolution)
- genetic interactions between pathogens and their hosts (orthologous sequences)


Netscape: Human Proteomics Initiative (HPI)
Back
Forward
Reload
Home
Search
Netscape
Images
Print
Security
Stop
Location:
http://www.expasy.ch/sprot/hpi/
What's Related
HPI Human Proteomics Initiative
We are initiating a major project to annotate all known human sequences according to the quality standards of SWISS-PROT. This means providing, for each known protein, a wealth of information that include the description of its function, its domain structure, subcellular location, post-translational modifications, variants, similarities to other proteins, etc.
The HPI project has two different time-related aspects: one of which is a nine-month "marathon" to catch up with the current state of research, the other one is a long-term commitment to keep such a project alive as long as it is necessary. A detailed description of the HPI initiative is provided below.
Detailed description of HPI
Current status of HPI
SWISS-PROT documents relevant to HPI
Index of MIM entries referenced in SWISS-PROT
Index of human proteins with sequence variants
Human chromosome 8 entries
new
Human chromosome 9 entries
new
Human chromosome 10 entries
new
Human chromosome 11 entries
new
Human chromosome 12 entries
Human chromosome 14 entries
Human chromosome 15 entries

Specialty of 2D Electrophoresis.




Netscape: BDGP: cDNAs & ESTs
Back
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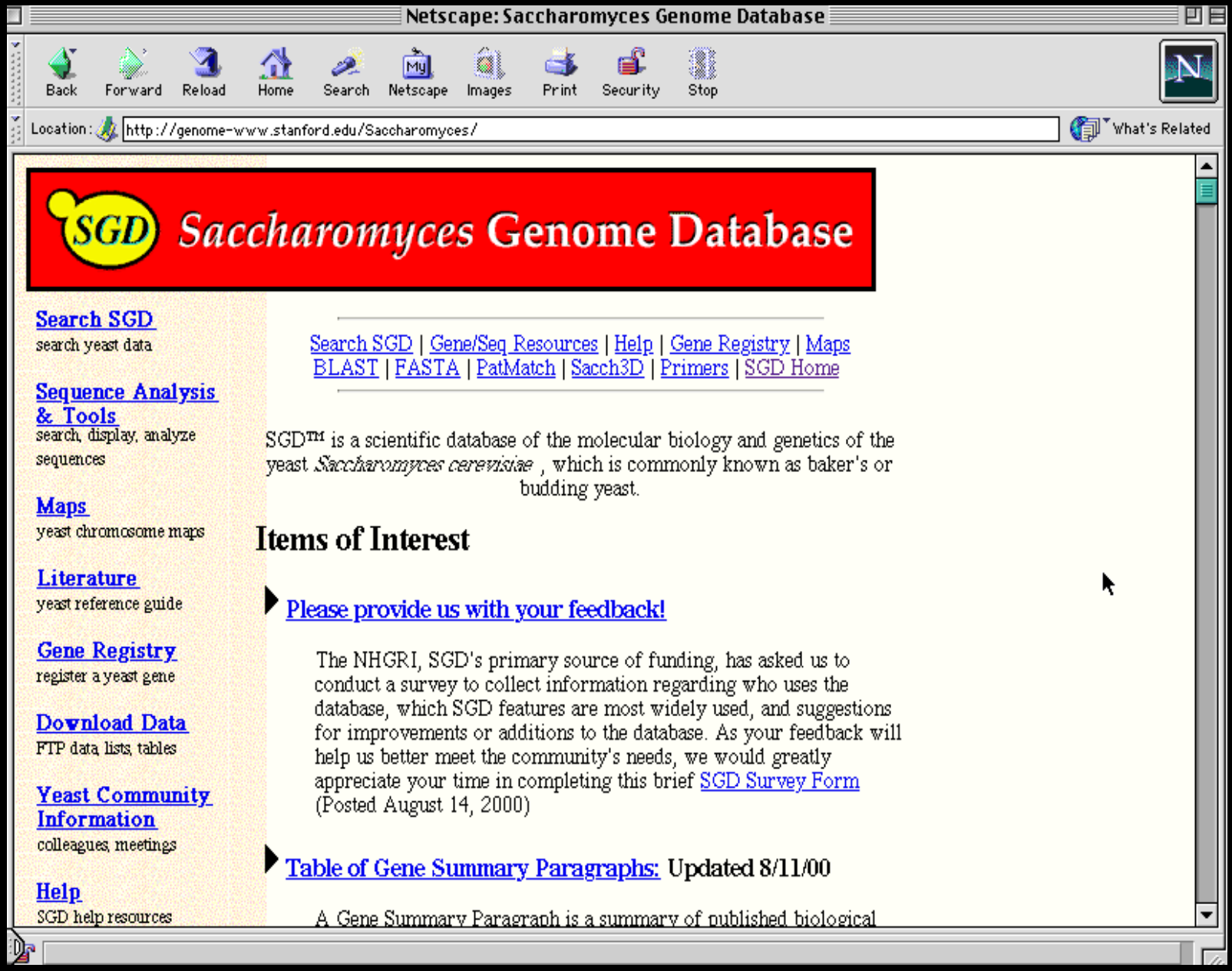
Security
Stop
Location: http://www.fruitfly.org/EST/index.html
What's Related
BDGP
Berkeley Drosophila Genome Project
Projects
Home
About BDGP
Employment, Contact Information, News, Citing BDGP
Searches
Fly BLAST
GadFly
Genome Annotations
Berkeley Fly Database
Clones, Sequences, Insertions
Map Viewers
cDNAs & ESTs
Drosophila Gene Collection
Full Insert Sequencing of the DGC Release 1.0
Old EST Project
New EST Project
CK EST Project
This project used cDNA sequencing to screen for novel secreted and transmembrane proteins important during development.
This work is now complete.
Search by Identifier
Search by GenBank or dbEST accession number, or BDGP clone ID or clot ID. Clots are groups of highly homologous EST sequences


Netscape: Saccharomyces Genome Database
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Home
Search
Netscape
Images
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Security
Stop
Location: http://genome-www.stanford.edu/Saccharomyces/
What's Related
SGD Saccharomyces Genome Database
Search SGD
search yeast data
Sequence Analysis & Tools
search, display, analyze sequences
Maps
yeast chromosome maps
Literature
yeast reference guide
Gene Registry
register a yeast gene
Download Data
FTP data, lists, tables
Yeast Community Information
colleagues, meetings
Help
SGD help resources
Search SGD | Gene/Seq Resources | Help | Gene Registry | Maps
BLAST | FASTA | PatMatch | Sacch3D | Primers | SGD Home
SGD™ is a scientific database of the molecular biology and genetics of the yeast Saccharomyces cerevisiae , which is commonly known as baker's or budding yeast.
Items of Interest
Please provide us with your feedback!
The NHGRI, SGD's primary source of funding, has asked us to conduct a survey to collect information regarding who uses the database, which SGD features are most widely used, and suggestions for improvements or additions to the database. As your feedback will help us better meet the community's needs, we would greatly appreciate your time in completing this brief SGD Survey Form (Posted August 14, 2000)
Table of Gene Summary Paragraphs: Updated 8/11/00
A Gene Summary Paragraph is a summary of published biological

The Zebrafish Information Network

Anatomical Atlases
- General information
- Anatomical parts list
- Developmental atlas
- Developmental Staging Series

Genetic Strains
- Deficiency strains
- Mutant and wild-type strains
- Laboratory Allele designations
- Nomenclature conventions
- Nomenclature committee
- Obtaining approval for gene names

Informatics
- Zebrafish Database Project
- ZFIN

Genomics & the Zebrafish Genome Initiative
- News & Updates
- Trans NIH Zebrafish Initiative
- Consolidated maps
- Conserved syntenies
- EST database
- Genes
- Meiotic maps
- SSLP database
- Other genomes

News and Information
- Cold Spring Harbor Meeting, 2000
- News, Updates, Jobs and Postings
- The Zebrafish Book
- The Zebrafish Science Monitor
- Zebrafish newsgroup

Molecular Probes
- Summary & links

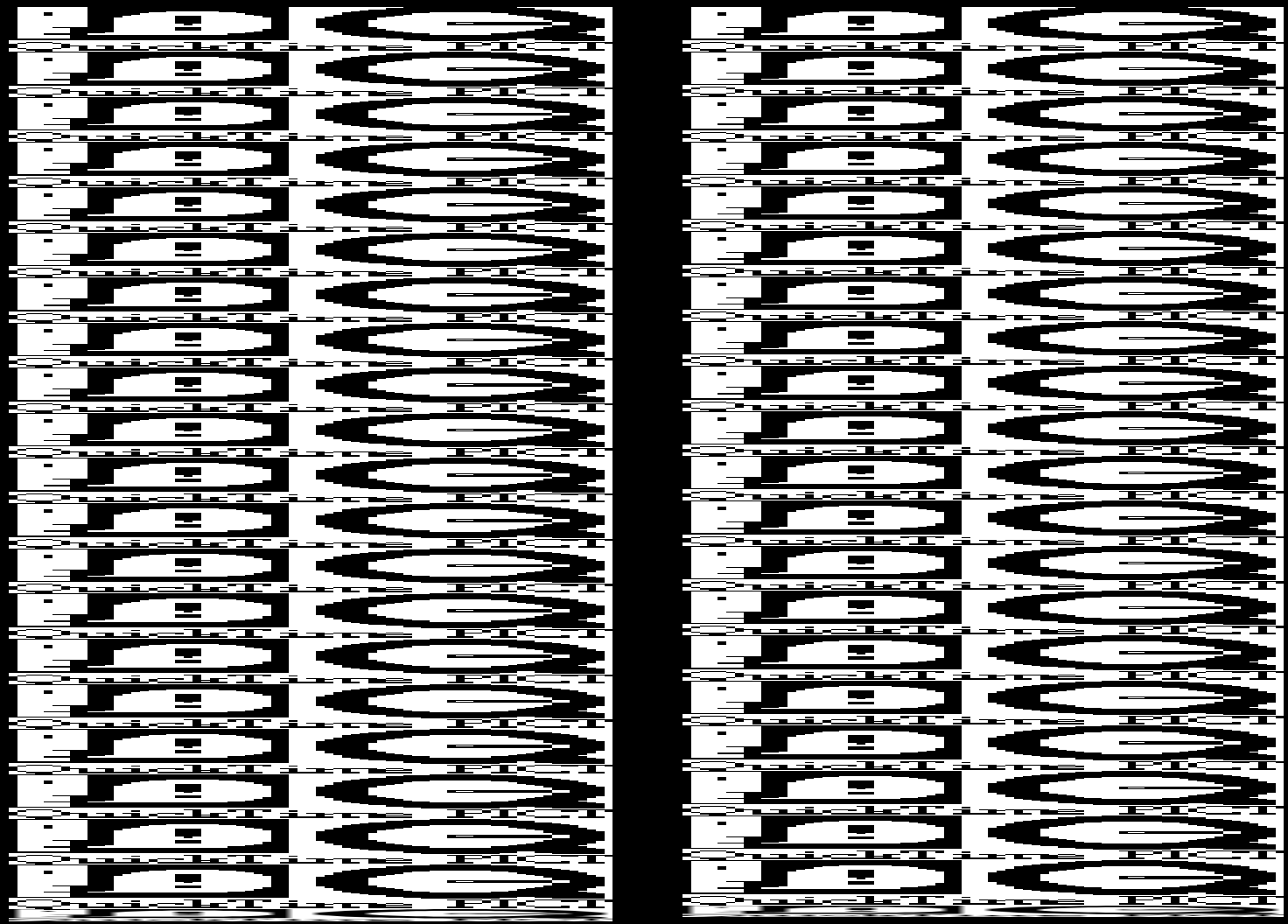
Publications and Community
- Laboratory contacts
- Researcher contacts
- Zebrafish publications
- Zebrafish for K-12

The Zebrafish Resource Center
- General information
- Availability of strains
- Histology services
- Pathology services
- Other Stock Centers

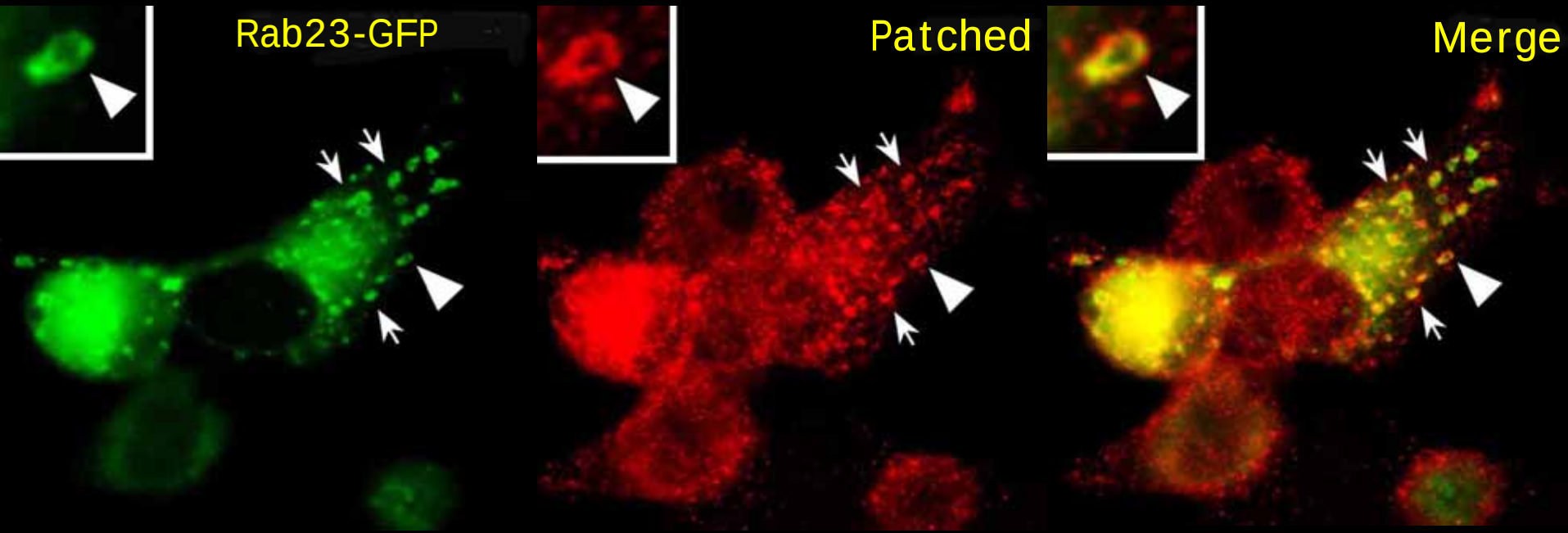
SEARCH this website

Functional Genomics

Patched gene expression in developing hair follicle

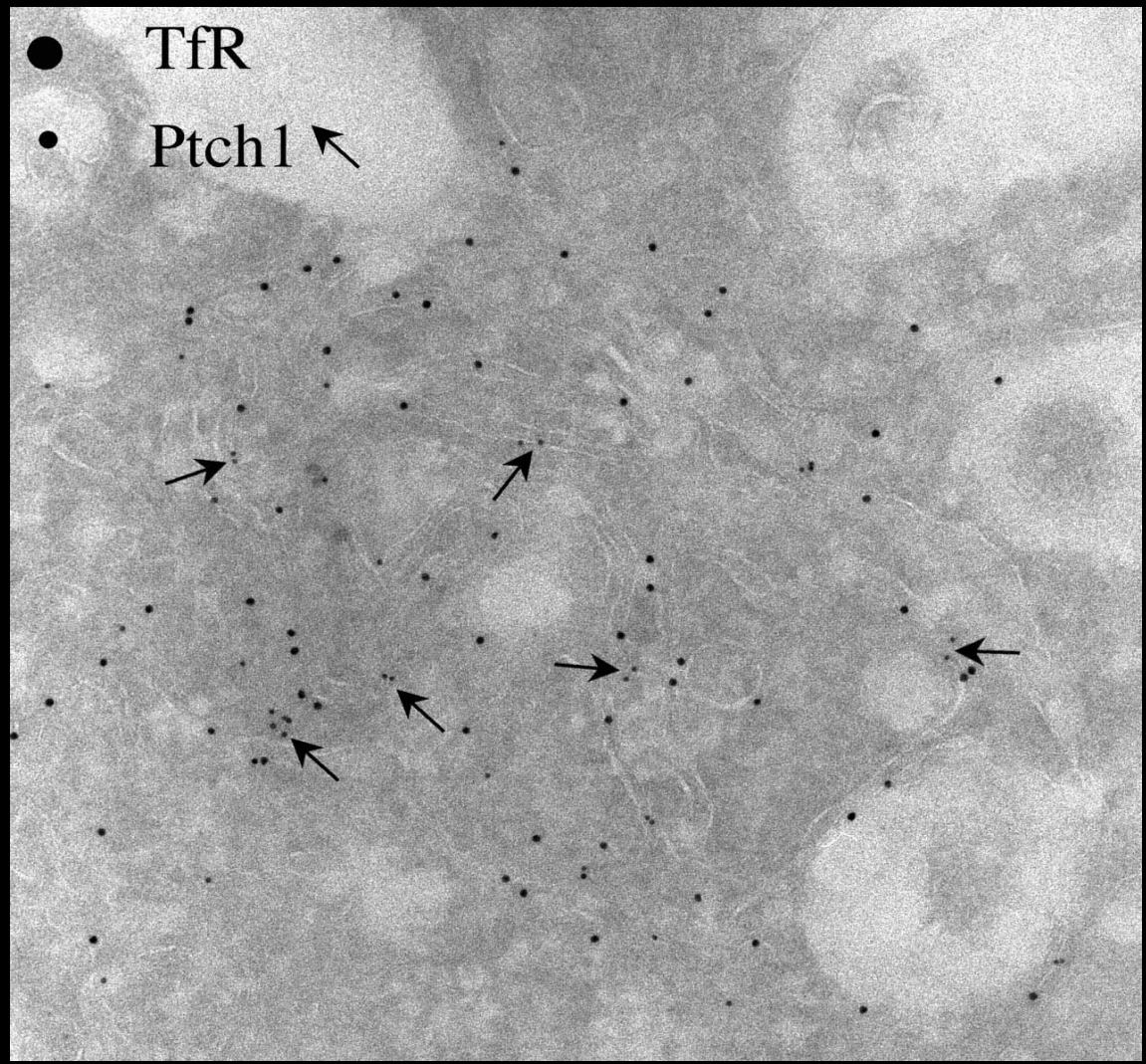


Transfected Patched co-localises with Rab23

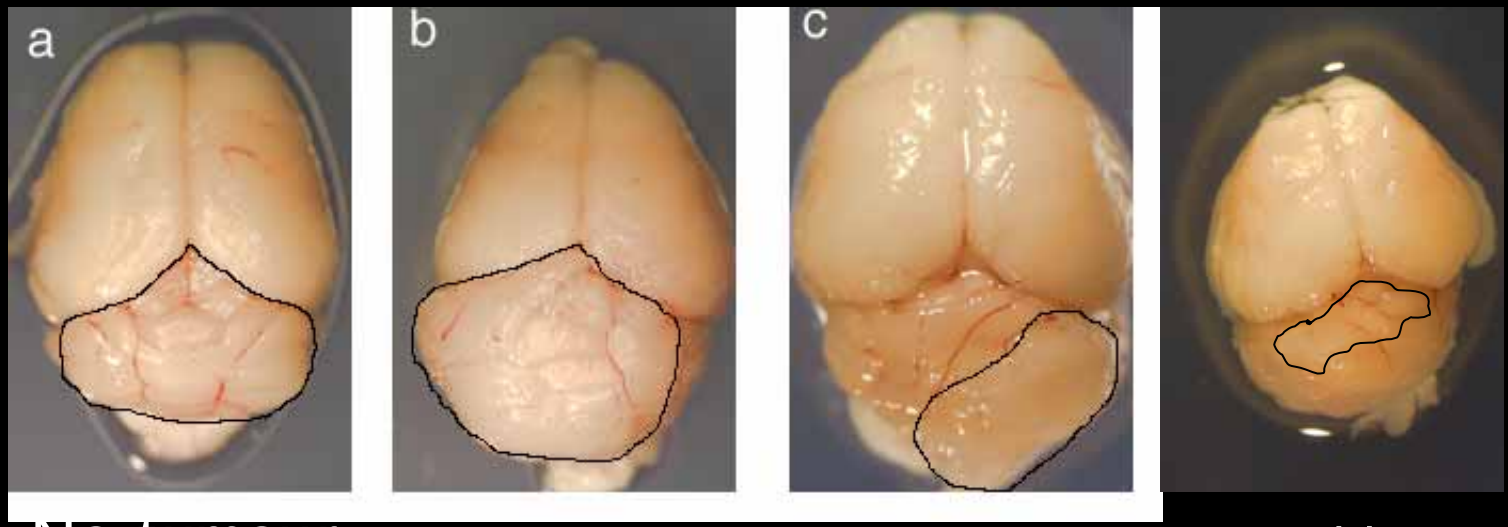


BHK-21 **Patched / Rab23-GFP**

Patched localisation to recycling endosomes supported by co-localisation with transferrin receptor



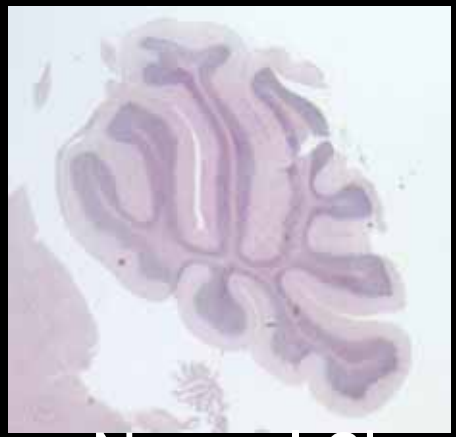
$Ptc^{neo/+;}$Ncre Brains



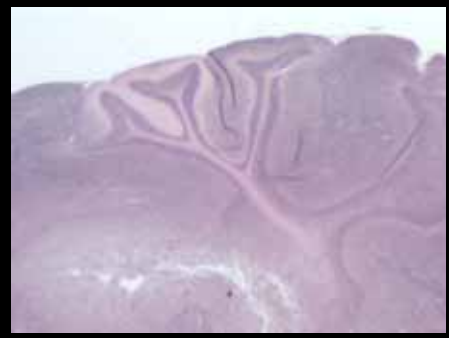
No tumour

+/△ Ncre

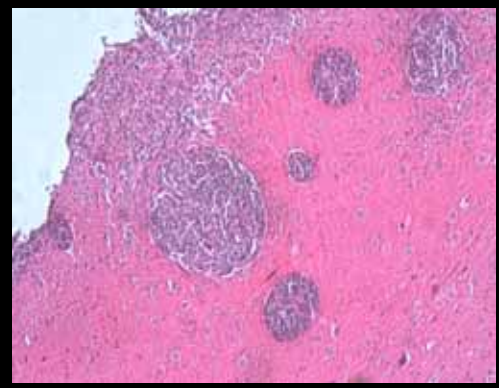
+/△ Ubiq cre



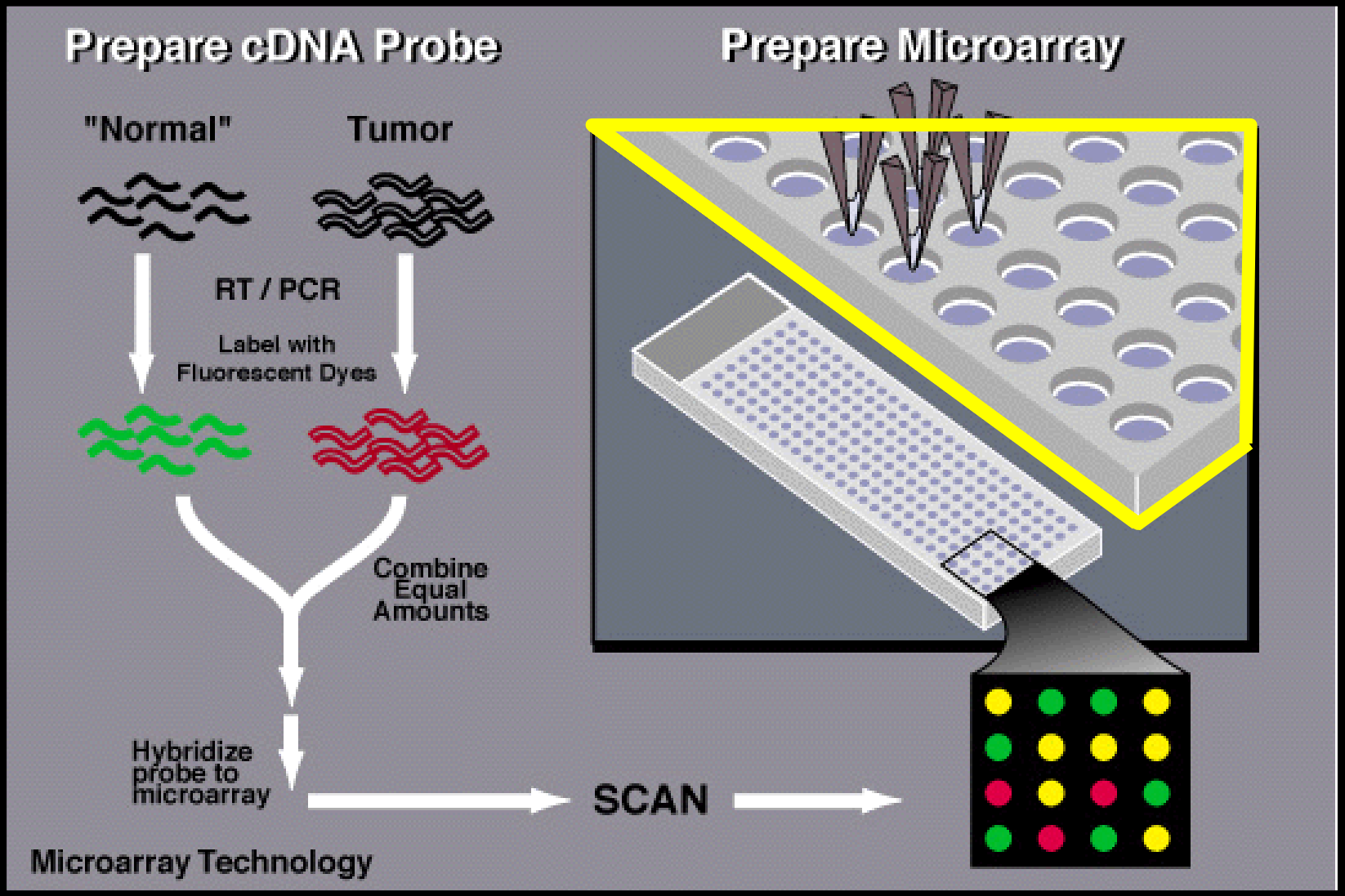
Normal Cb

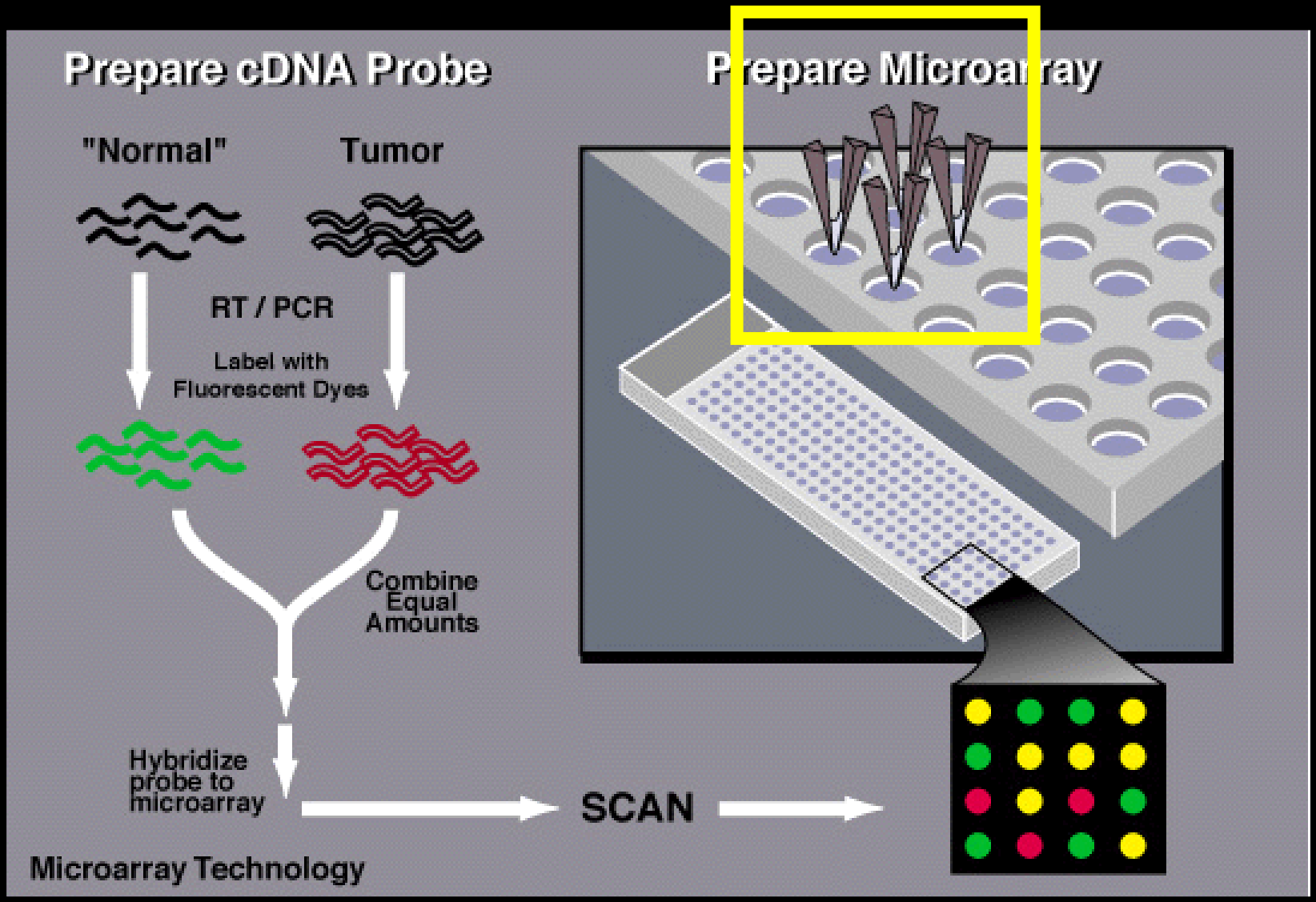


tumour

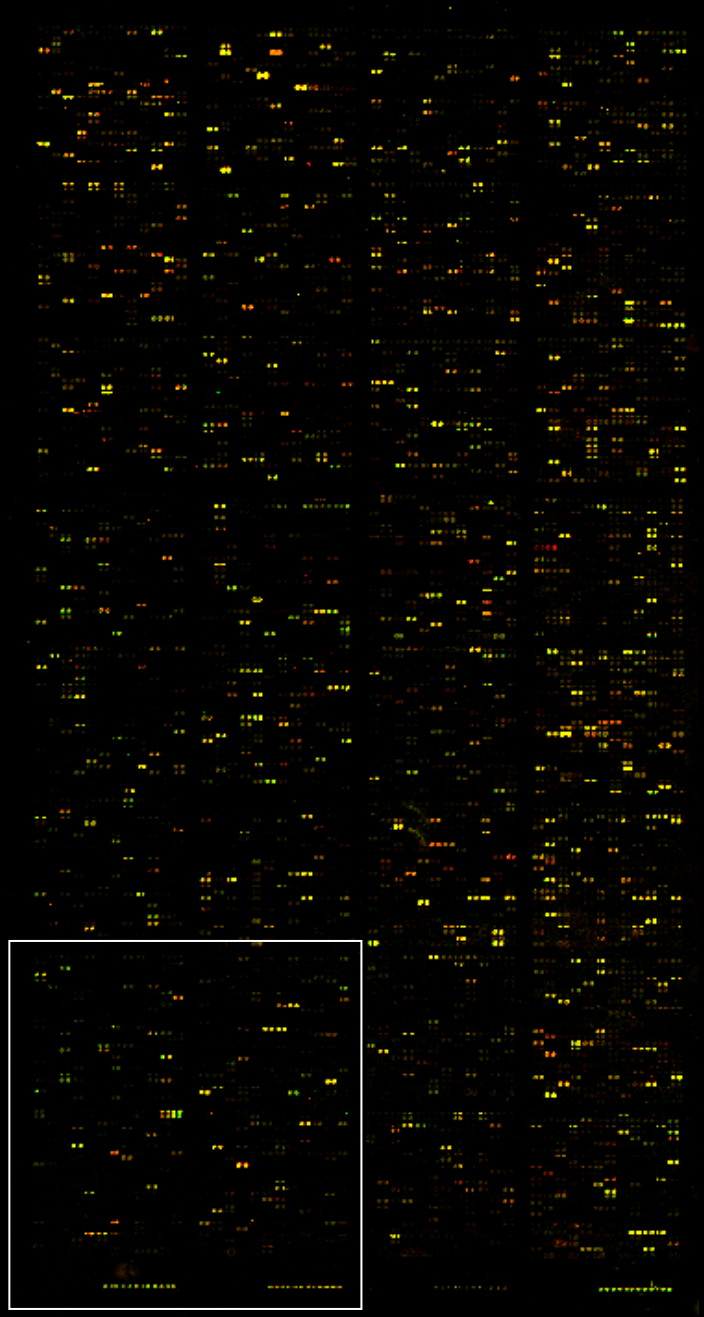


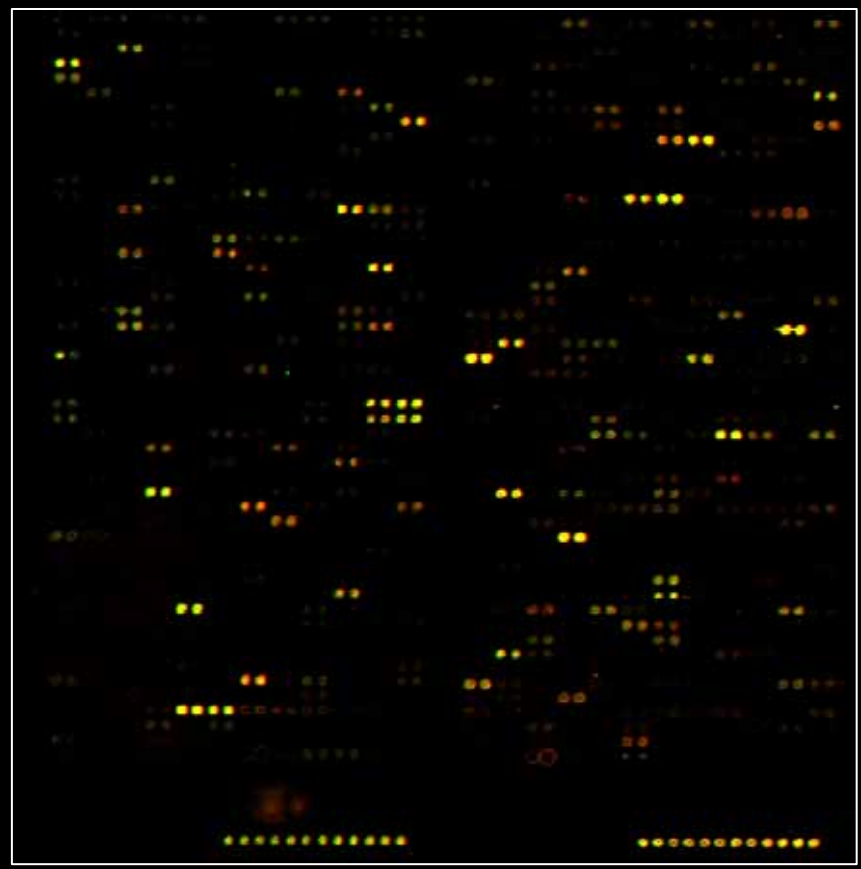
Infiltrating tumour

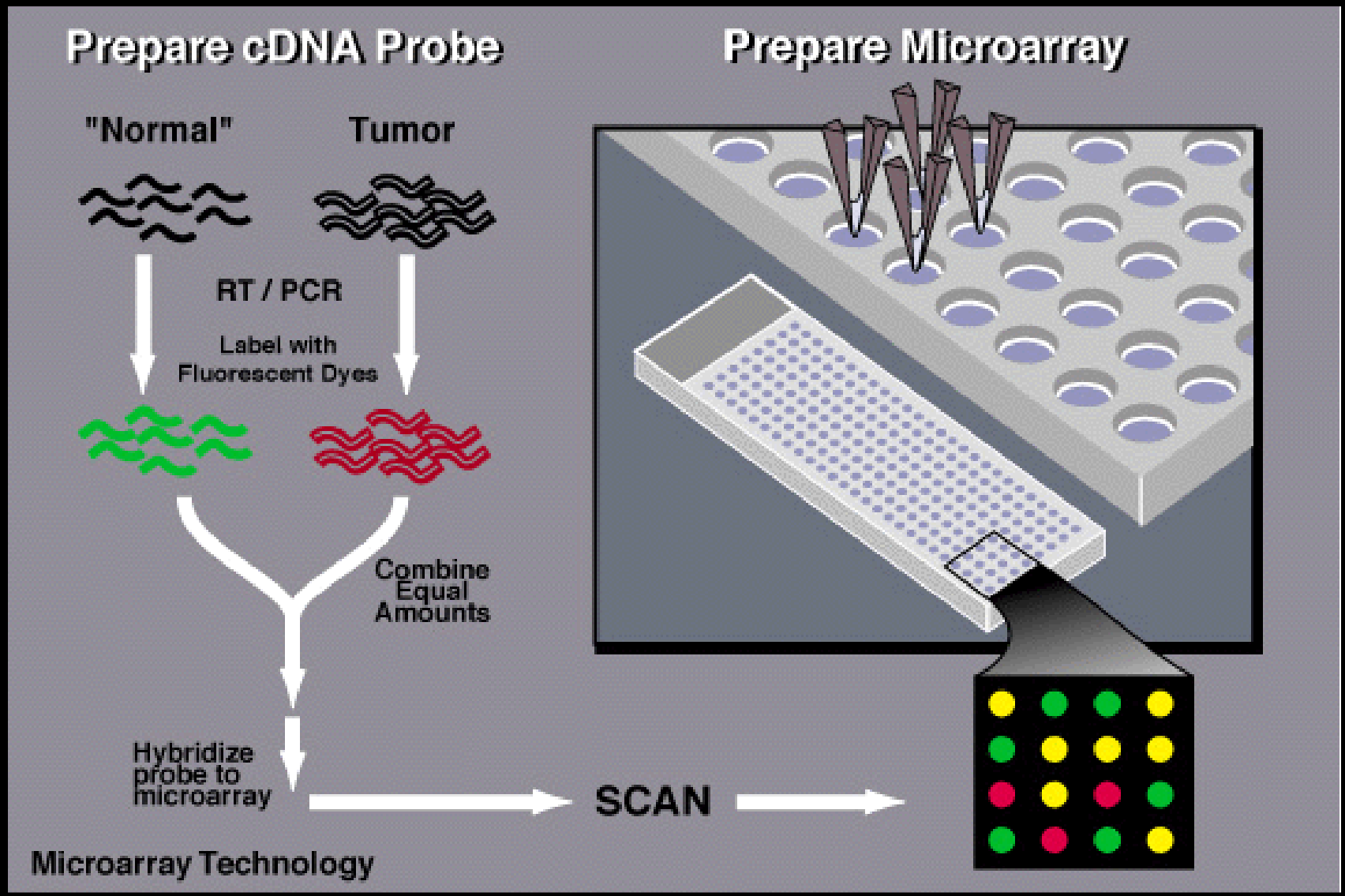

Prepare cDNA Probe
Prepare Microarray
"Normal"
Tumor
RT / PCR
Label with
Fluorescent Dyes
Combine
Equal
Amounts
Hybridize
probe to
microarray
SCAN
Microarray Technology


Prepare cDNA Probe
Prepare Microarray
"Normal"
Tumor
RT / PCR
Label with
Fluorescent Dyes
Combine
Equal
Amounts
Hybridize
probe to
microarray
SCAN
Microarray Technology

19K Human cDNA microarray



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SCAN
Microarray Technology

norms
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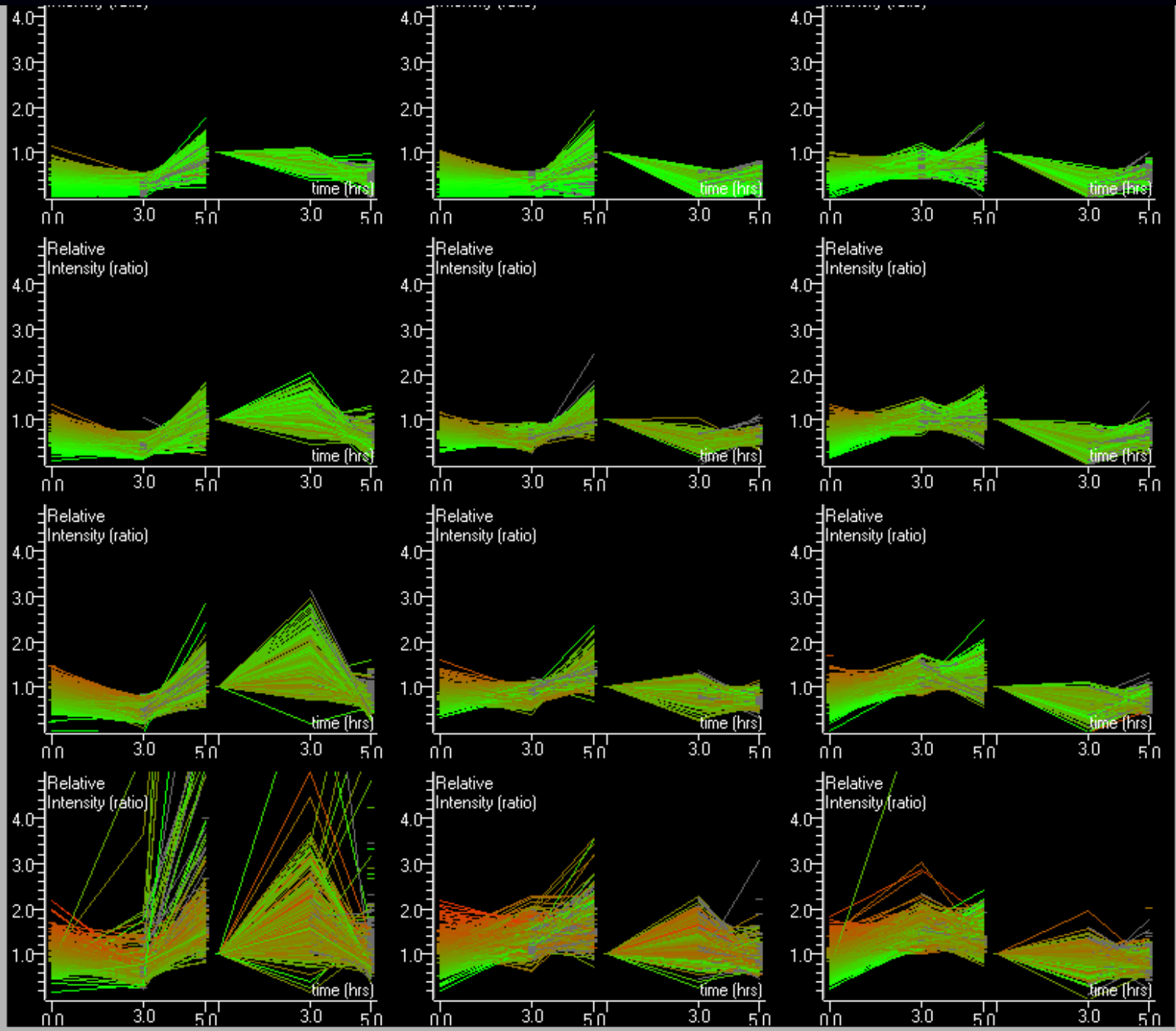


Expression

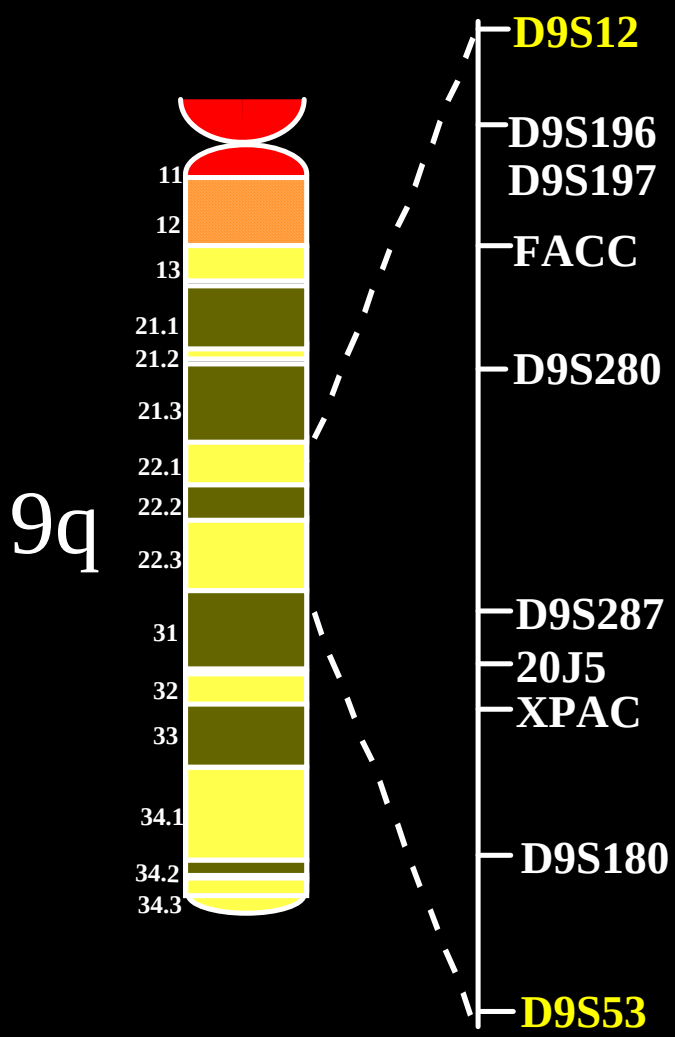
time 0 hrs CF

Medical Impact of Genomics Research

- Drug candidates (proteins)
- Gene therapy
- Target identification & validation and subsequent small molecule drug discovery
- Pharmacogenomics and drug development
- Diagnosis and disease management

Success Rates

- new drug: >$US600 million
- time line is 12-15 years
- 5% compounds tested enter preclinical trials
- 2% preclinical candidates enter clinical trials
- 80% drugs in Phase I fail


9q
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34.1
34.2
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D9S196
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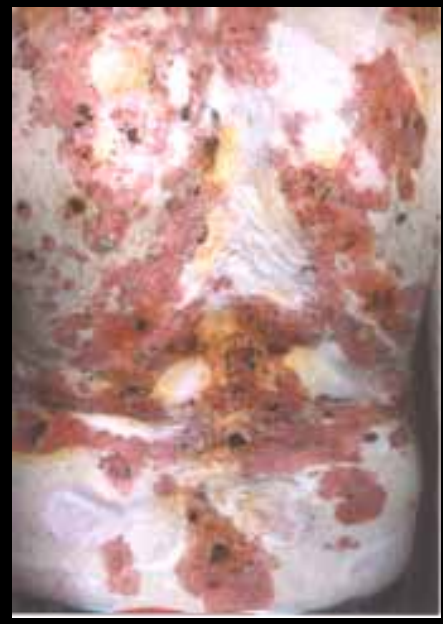
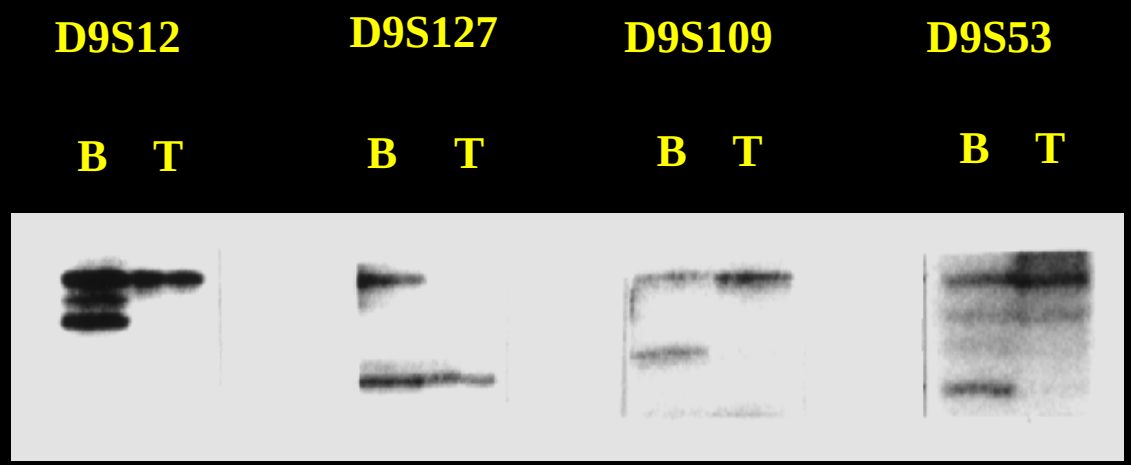
20J5
XPAC
D9S180
D9S53




D9S12
D9S127
D9S109
D9S53
B T
B T
B T
B T

The Challenge

"Most genetic traits in populations of humans and other organisms are determined by many factors, including genetic and environmental components, which interact in often unpredictable ways. For such complex traits, the whole is not only greater than the sum of its parts, it may be different from the sum of its parts. Thus, complex traits have an architecture that consists of all genetic and environmental factors that contribute to the trait, as well as their magnitude and theirinteractions. ……

The analysis of complex traits does not lend itself to quick and easy solutions"

“complex genetic traits”

Endometriosis
Multiple sclerosis
IDDM
BCC
Hypertension

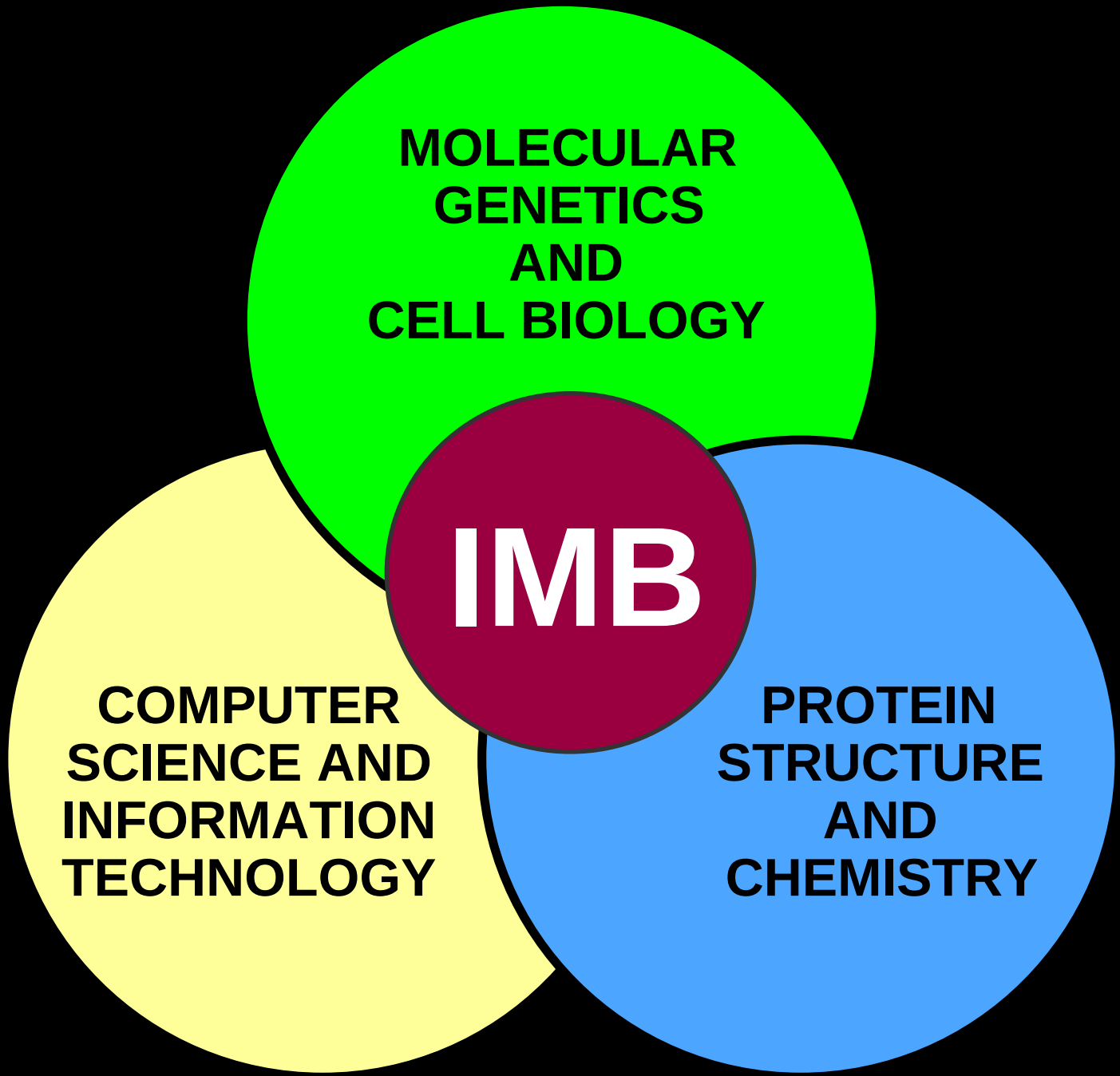
Nephropathy
Alcoholism
Menopausal age
Preclampsia
Uterine fibroids
Psoriasis

Eczema
ADHD
Fertility
Rheumatoid arthritis
Host/Parasite responsiveness
Osteoarthritis
NIDDM

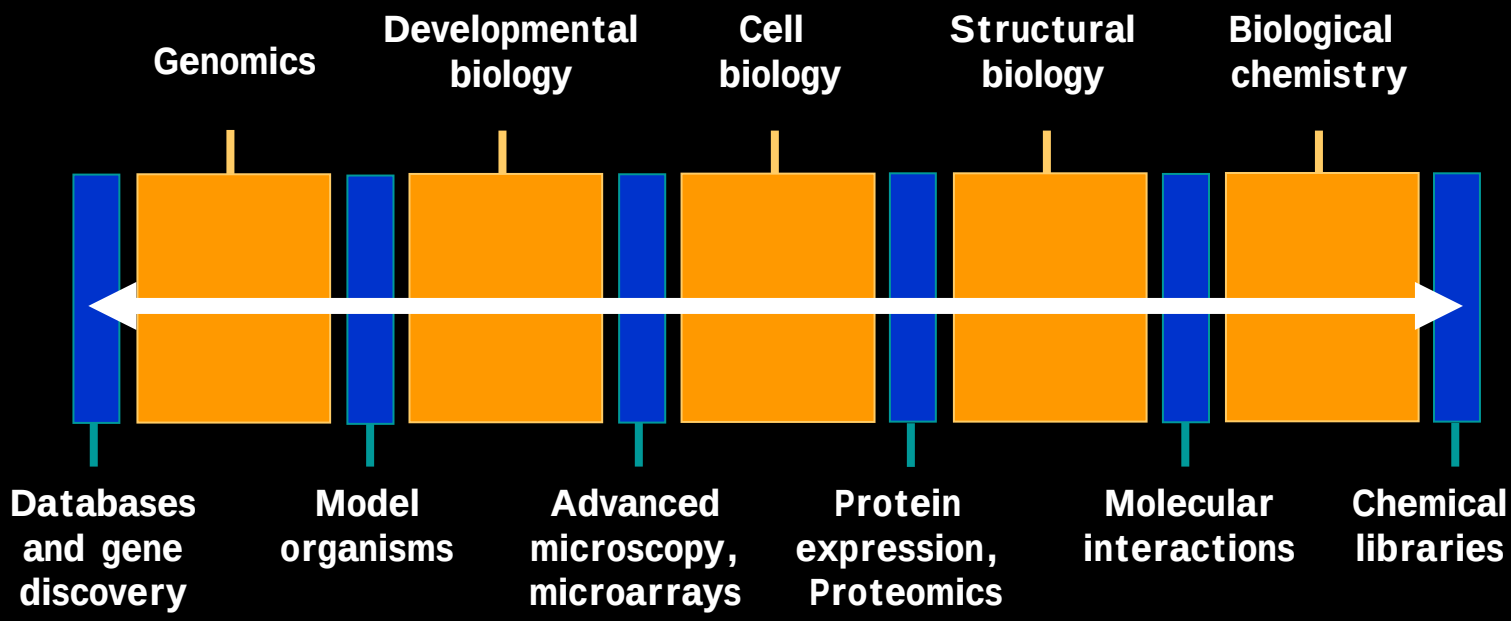
SNPs

- Common DNA sequence variation between individuals.
- Both private and publicly funded SNP projects.
- Utility for discerning the genetic basis of common human disease.

Website by dedicated.com


MOLECULAR
GENETICS
AND
CELL BIOLOGY
IMB
COMPUTER
SCIENCE AND
INFORMATION
TECHNOLOGY
PROTEIN
STRUCTURE
AND
CHEMISTRY

Systems Biology - The IMB Biodiscovery Pipeline

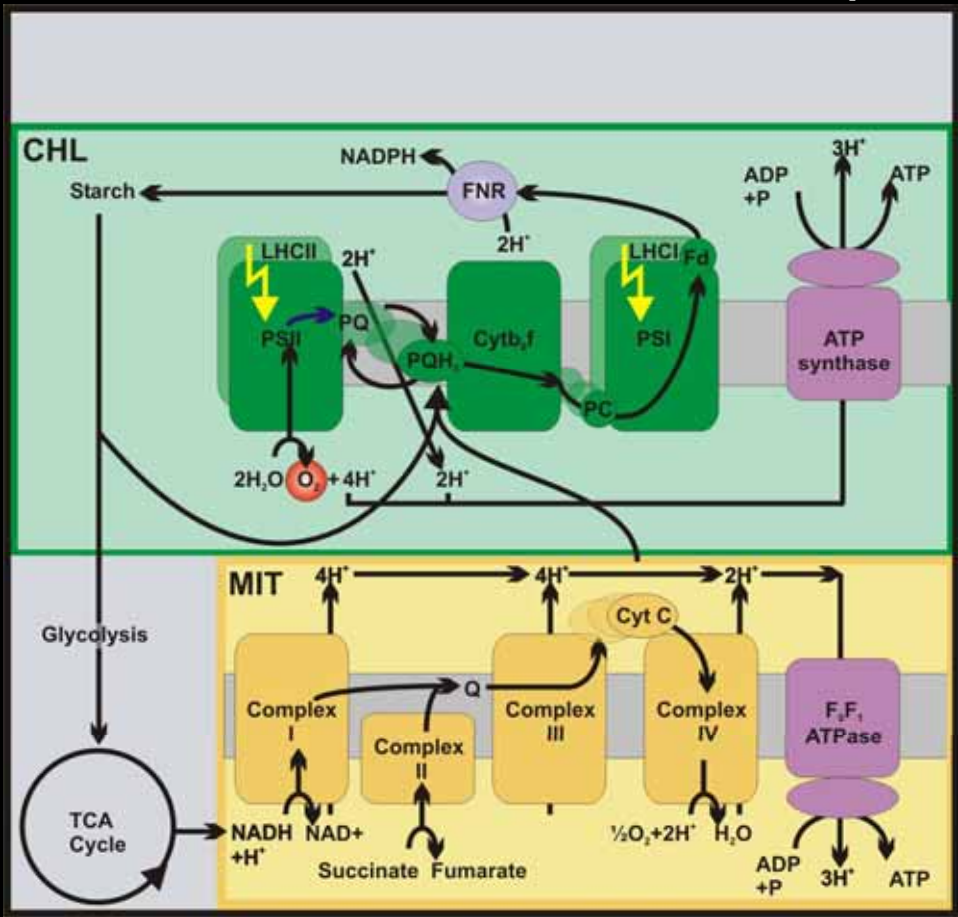


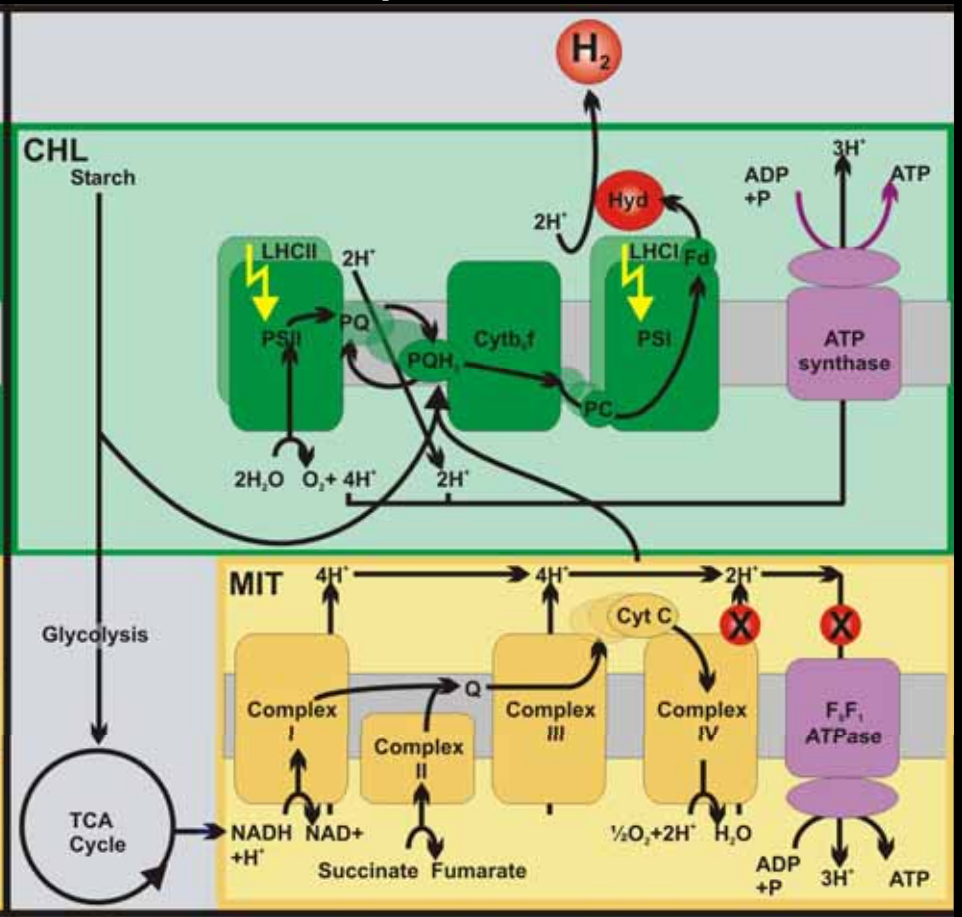
Bioinformatics and Computational Biology

imbcom pty ltd

the commercialisation company for the institute for molecular bioscience

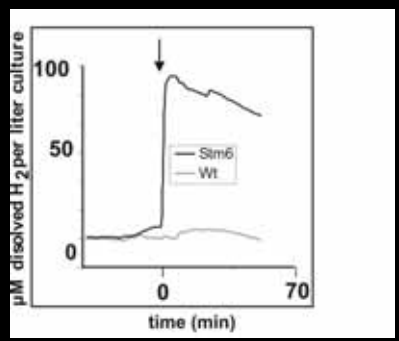
HIGH H_2 PRODUCING ALGAL MUTANT (PROVISIONAL PATENT) - KRUSE / HANKAMER



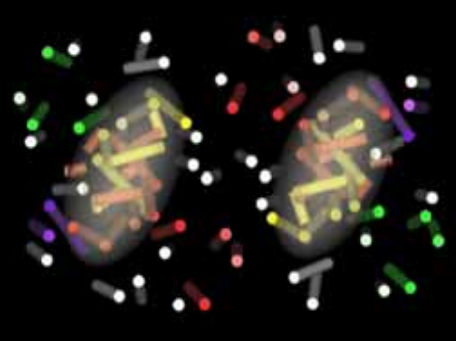


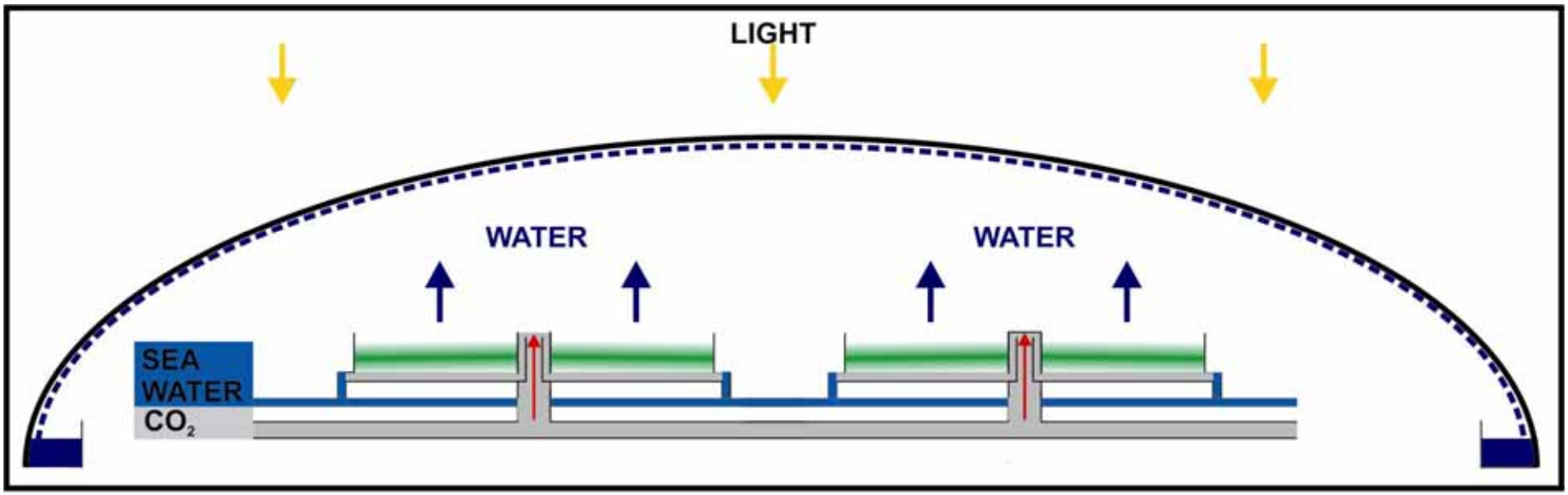
MOLECULAR BIOLOGY

CULTURE OPTIMIZATION



STRUCTURAL BIOLOGY



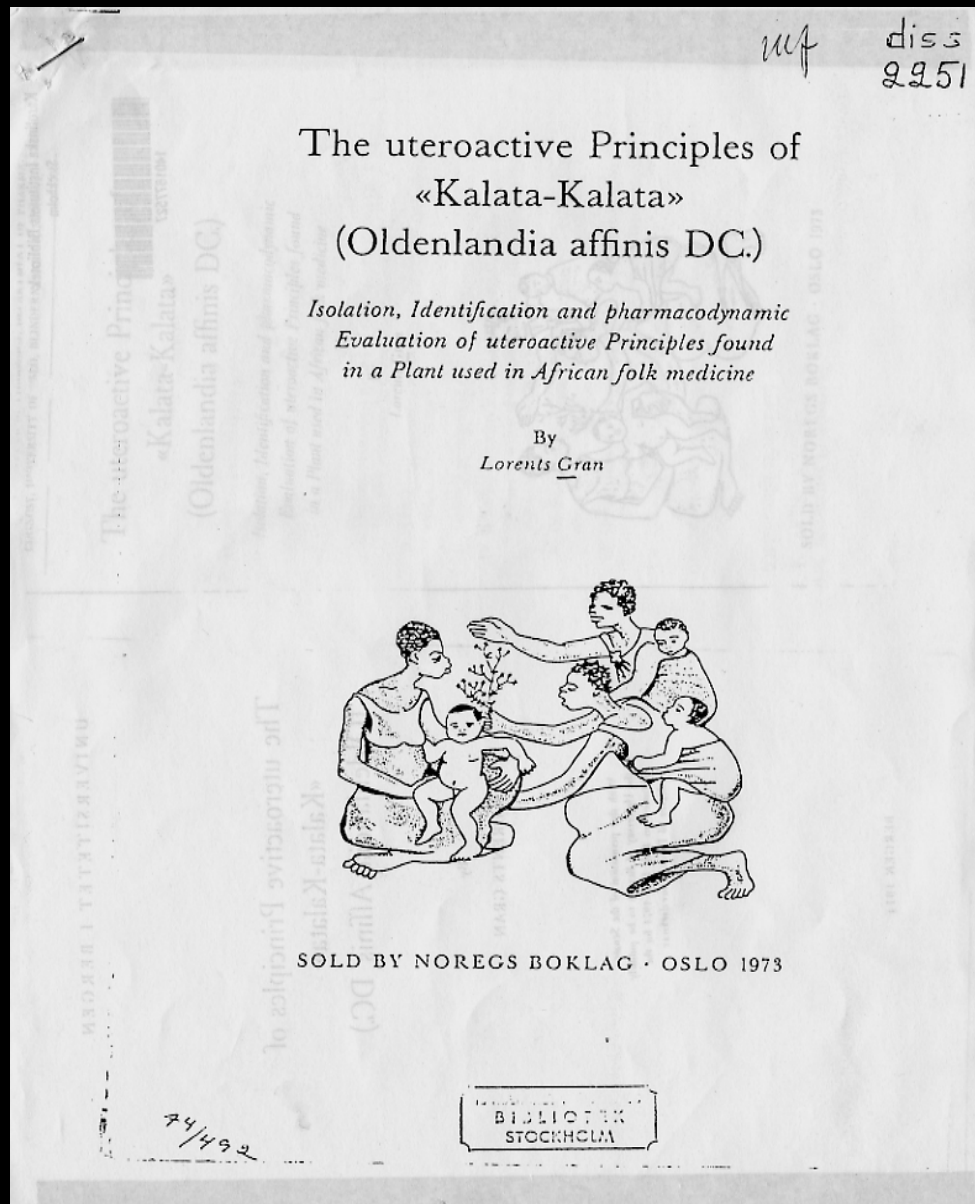


POTENTIAL BENEFITS

1) BIOMASS PRODUCTION: FEEDSTOCK FOR H_2, ETHANOL AND METHANOL PRODUCTION
2) SALT WATER TO FRESH WATER CONVERSION (EVAPORATION+ COMBUSTION)
3) C-SEQUESTRATION (LIMITED)

Cyclotides: Discovery

- Native medicine- uterotonic agent
- Prototypic member is kalata B1
- 29 amino acids, circular backbone
- Knotted disulfide topology



uf diss 2251

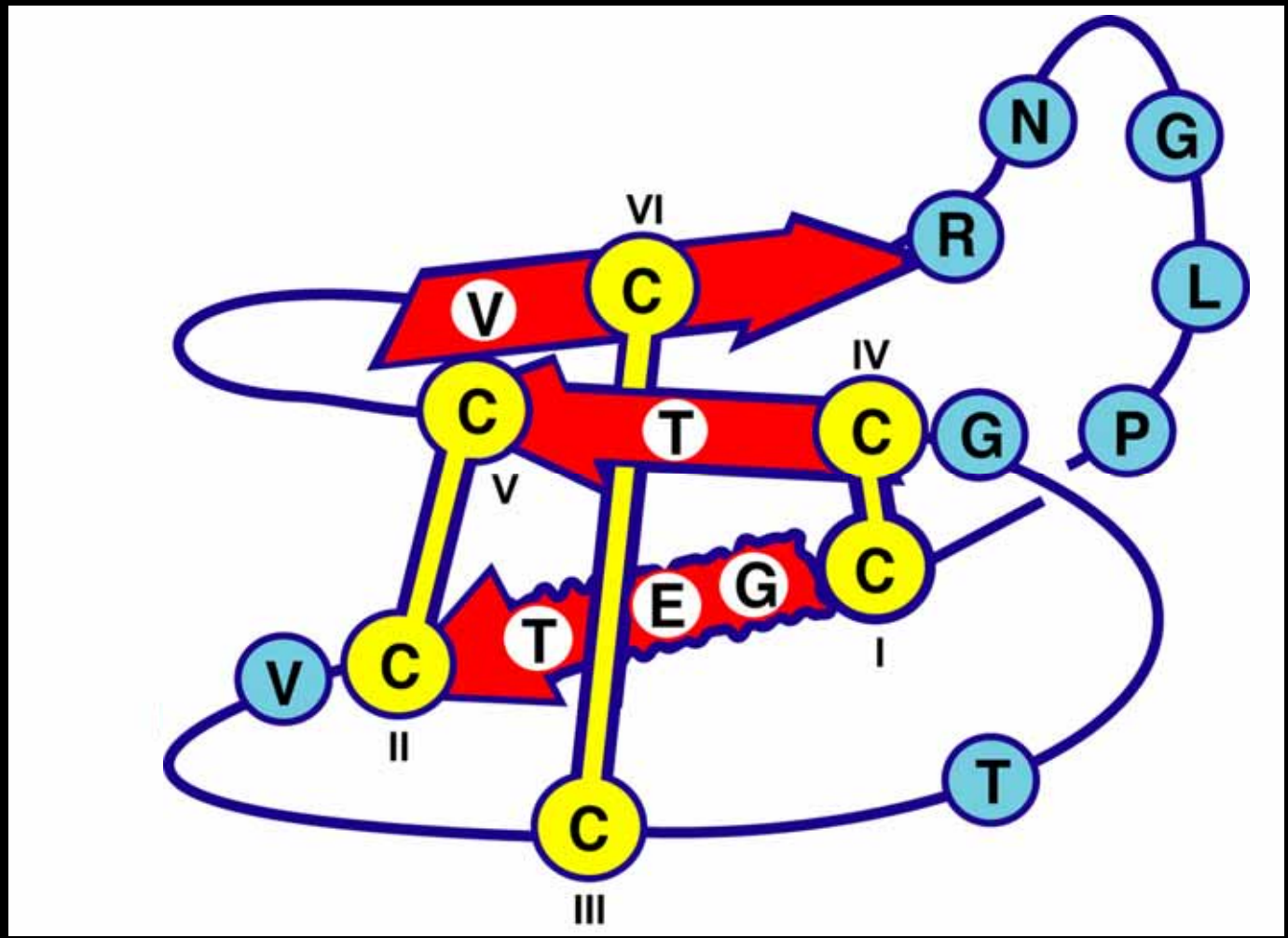
The uteroactive Principles of
«Kalata-Kalata»
(Oldenlandia affinis DC.)

Isolation, Identification and pharmacodynamic Evaluation of uteroactive Principles found in a Plant used in African folk medicine

By
Lorents Gran

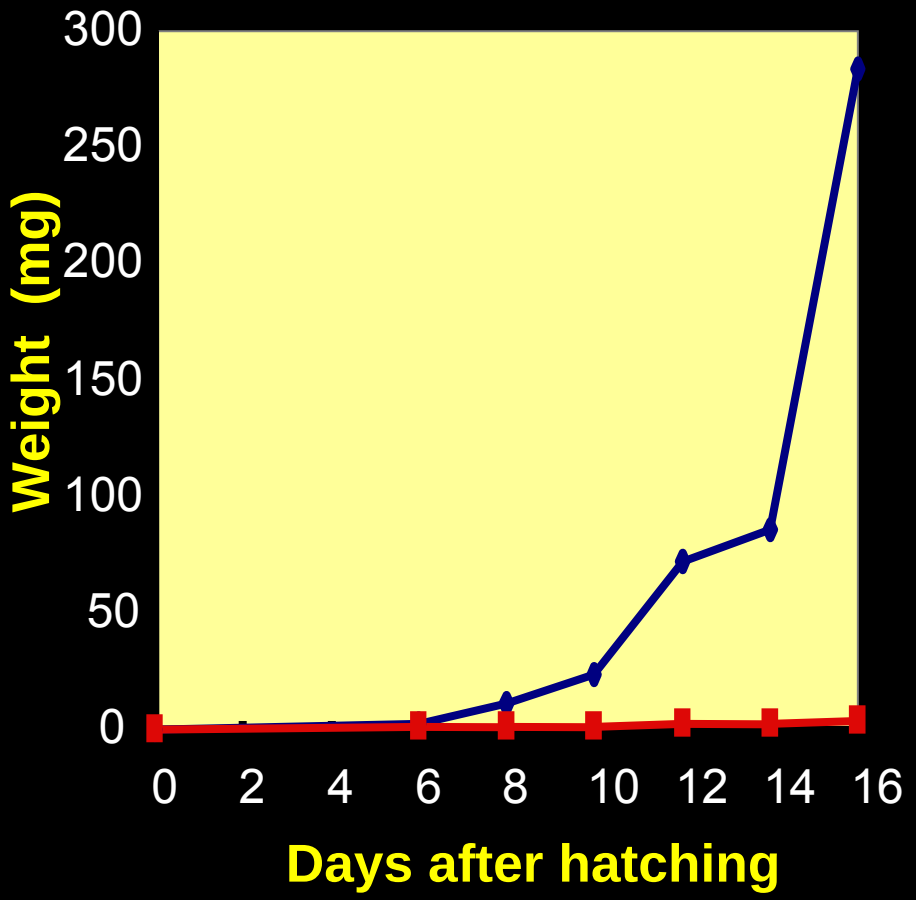
Kalata B1: a compact mini-protein

with a structurally conserved framework

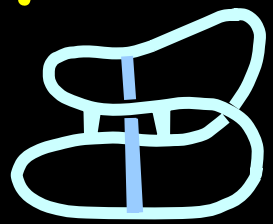


www.cyclotide.com

Larval growth +/- kalata B1



Cyclagen



- GM crops produced 1.8 billion kg more than conventional varieties
- Boosted farm incomes by $US1.5 billlion
- Cut pesticide usage by 20.8 million kg

National Centre for Food and Agricultural Policy, Bio2002, June 10 2002

- natural insecticides for plants
- plant-to-plant gene transfer

Thank you!