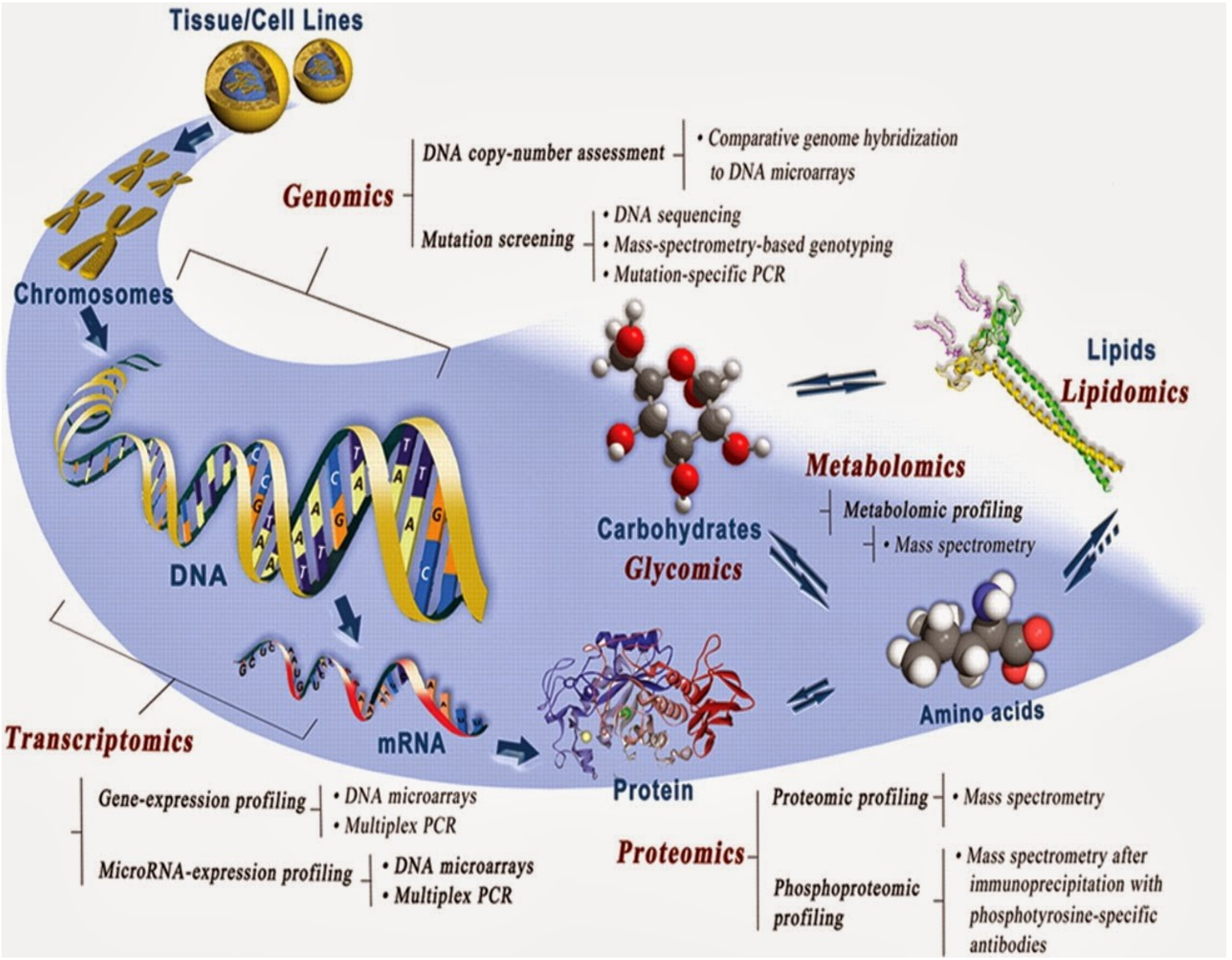
Omics


Tissue/Cell Lines
Chromosomes
Genomics
DNA copy-number assessment
• Comparative genome hybridization to DNA microarrays
Mutation screening
• DNA sequencing
• Mass-spectrometry-based genotyping
• Mutation-specific PCR
DNA
Transcriptomics
mRNA
Gene-expression profiling
• DNA microarrays
• Multiplex PCR
MicroRNA-expression profiling
• DNA microarrays
• Multiplex PCR
Protein
Proteomics
Proteomic profiling
• Mass spectrometry
Phosphoproteomic profiling
• Mass spectrometry after immunoprecipitation with phosphotyrosine-specific antibodies
Carbohydrates
Glycomics
Metabolomics
Metabolomic profiling
• Mass spectrometry
Lipids
Lipidomics
Amino acids

Exponential growth of data in biology

Storing large databases and providing access

Data types:

- Nucleotide sequences
- Protein sequences
- Protein sequence motifs and patterns
- Three-dimensional structure of macromolecules
- Gene expression data
- Metabolic pathways
- Disease related variations

==> ***Bioinformatics ==> BIG DATA***

Biological databases

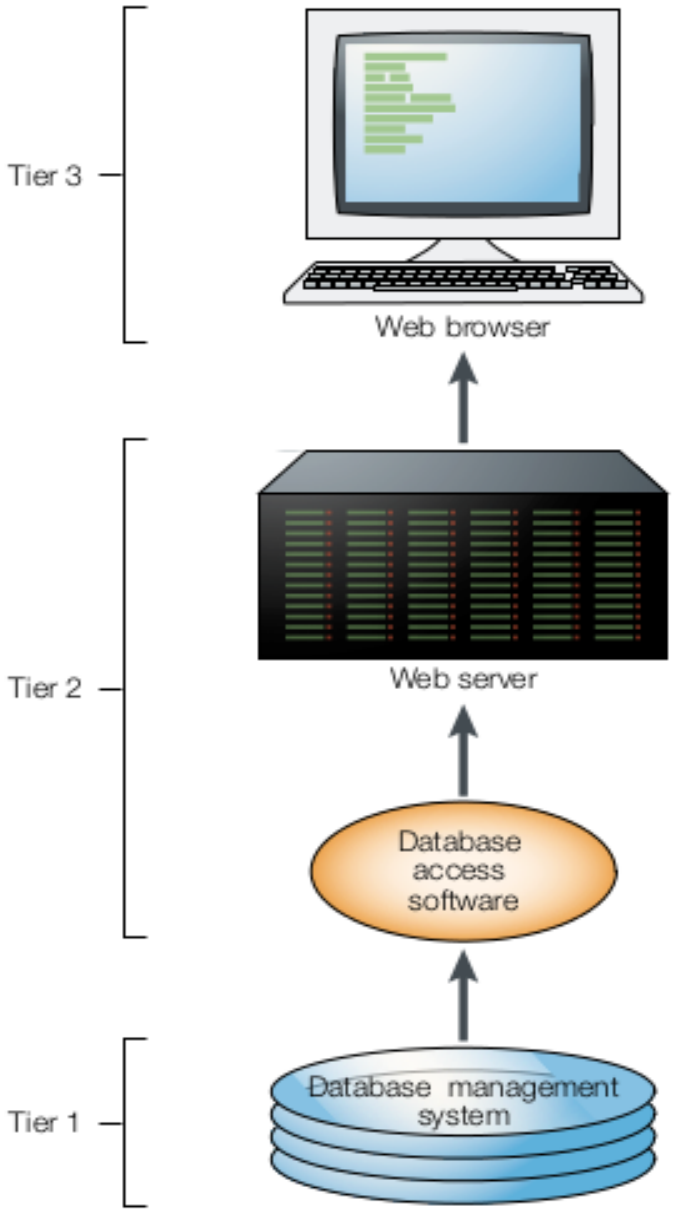


Figure 1 | **Biological database architecture.** Most biological databases use a three-tier architecture that consists of a database management system, a middleware layer and a web interface.

Three basic requirements:

1. Ready access to the collected pool of information

2. An easy way to extract and manipulate data quickly

3. Enough computing power and storage capacity.

Updates and revisions

- Data entry and quality checks
- Researchers (groups) enter the data
- Curators add and update the data

- Marking and removing wrong data
- Types and extent of checking
- Consistency, redundancy, updates

Updates and revisions

Bioinformatics tools and databases can change with time!

- Save the data locally
  e.g. identifiers, sequences

Bioinformatics tools

There is a great number of bioinformatics tools

- First check, if there is a tool already exists for your problem
- Don't worry if you don't know all the tools

Good starting points: NAR Database and Web Servers Issues

- Convergence of resources

Questions

- Which proteins belong to a given gene?
- What is their known function?
- What kind of diseases it is associated with?

- NCBI
- UNIPROT
- ENSEMBL

Name and identifier

Identifier

Entry name in Uniprot (pl. ADH6_HUMAN)
Locus in GenBank (pl. HUMADH6A01)

Accession number

Unique
Does not change

P28322 (Uniprot)
AH001409 (Genbank)
ENSG00000172955 (ENSEMBL)

Version number

Names

Rad24 in *Saccharomyces cerevisiae* (budding yeast)
the DNA-damage checkpoint-pathway gene

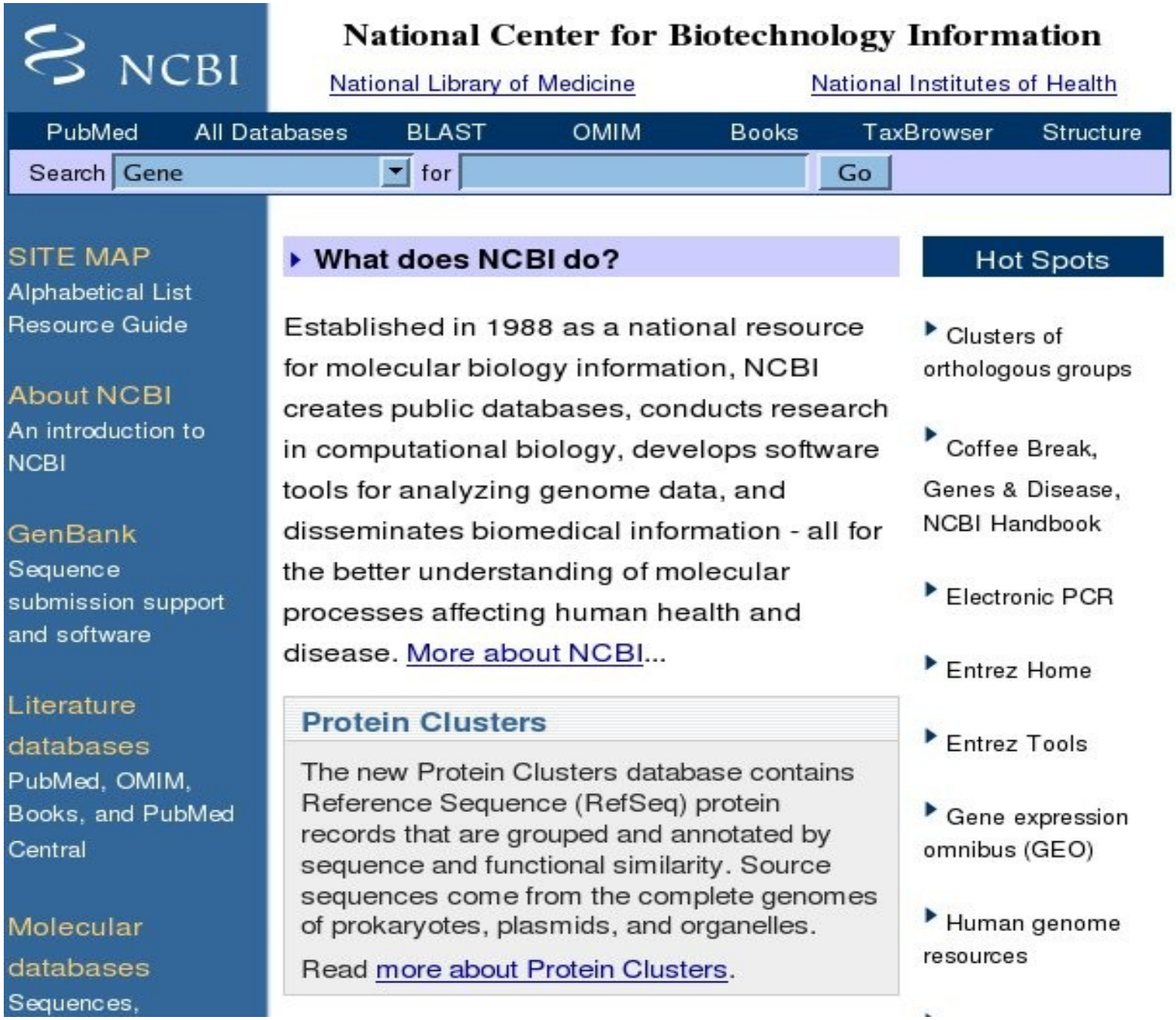
Rad24 in *Saccharomyces pombe* (fission yeast)
is involved in the checkpoint pathway,

BUT it is not ortholog of S. cerevisiae Rad24

The correct *S. pombe* orthilog is **rad17**, which is not the same as the **Rad17** gene in *S. cerevisiae*.

There are severl rad gene in C. elegans but these are not orthologs of the *S. cerevisiae* Rad17. The closest relative of this gene is mrt-2.

Sequence databases: NCBI



Sequence databases: Genbank

GenBank ® is the NIH genetic sequence database, an annotated collection of all publicly available DNA sequences

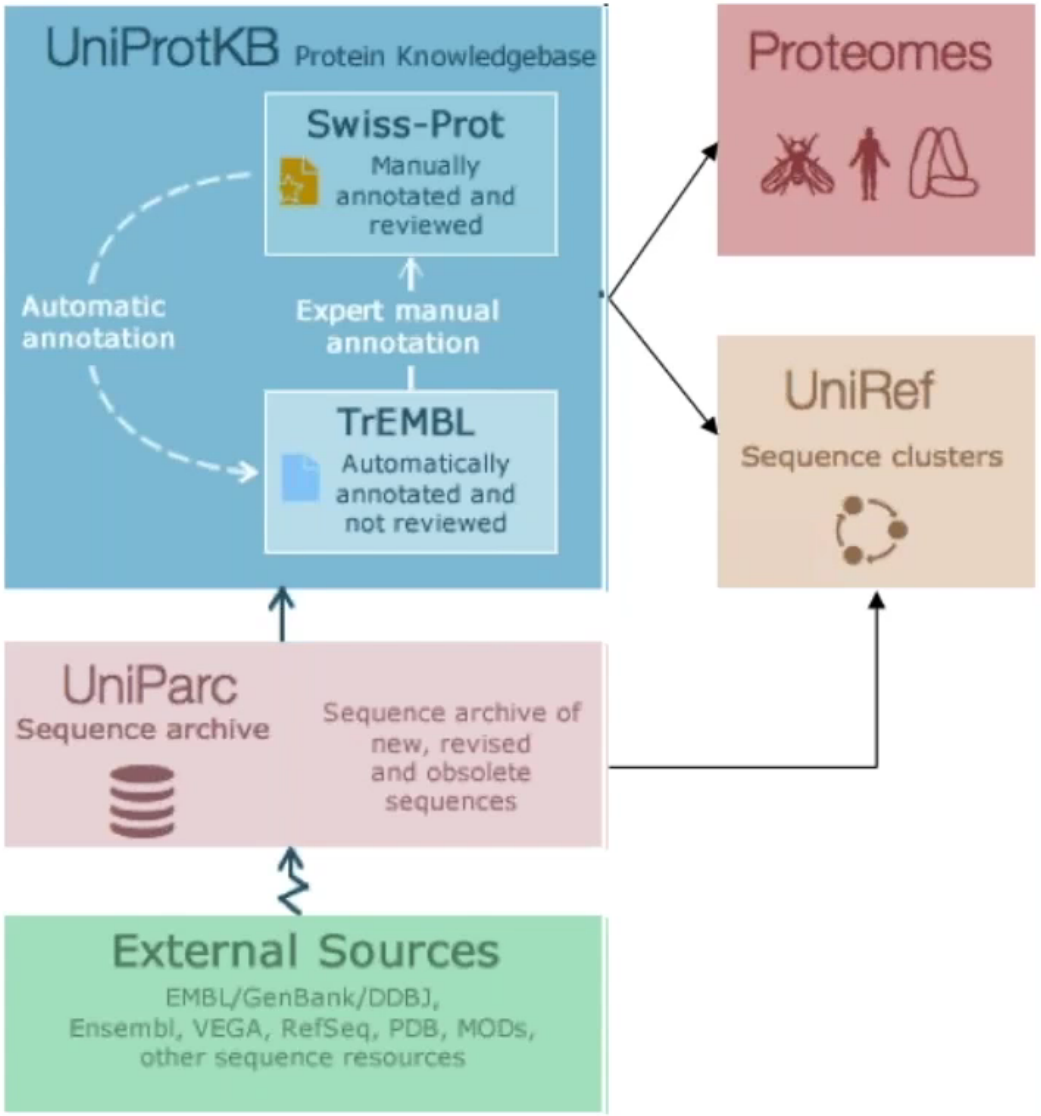
GenBank is accessible through the NCBI Entrez retrieval system, which integrates data from the major **DNA and protein sequence databases** along with taxonomy, genome, mapping, protein structure and domain information, and the biomedical journal literature via PubMed.

Genbank flat file

Filtered data in the RefSeq database but not in GenBank.

UniProt (Knowledgebase)

- millions of protein sequences
- experimental information extracted from scientific literature
- provision of complete and up to date Reference proteomes
- integration of large-scale genomics and proteomics experiments
- interoperability between data and services in the biological, medical, translational and clinical domains



Uniprot: SwissProt+TrEMBL

UniProt (Universal Protein): A central repository of **protein sequence** and function

Swiss-Prot

- The protein sequence database that contains core data enhanced by manually curated annotation.

Swiss-Prot annotation describes features such as function, post-translational modifications, domains and sites, secondary and quaternary structure, diseases, and sequence variants.

TrEMBL

The computer-annotated section of UNIPROT

Contains translations of all coding regions and sequences extracted from literature.

The quality of the data is dependent upon the information provided by the submitter of the nucleotide data.

Enhanced through redundancy removal, and automatic annotation

Swissprot/TrEMBL

UniProtKB/Swiss-Prot

- Non-redundant
- High level of integration
- High level of manual curation
- Contains 550116 entries

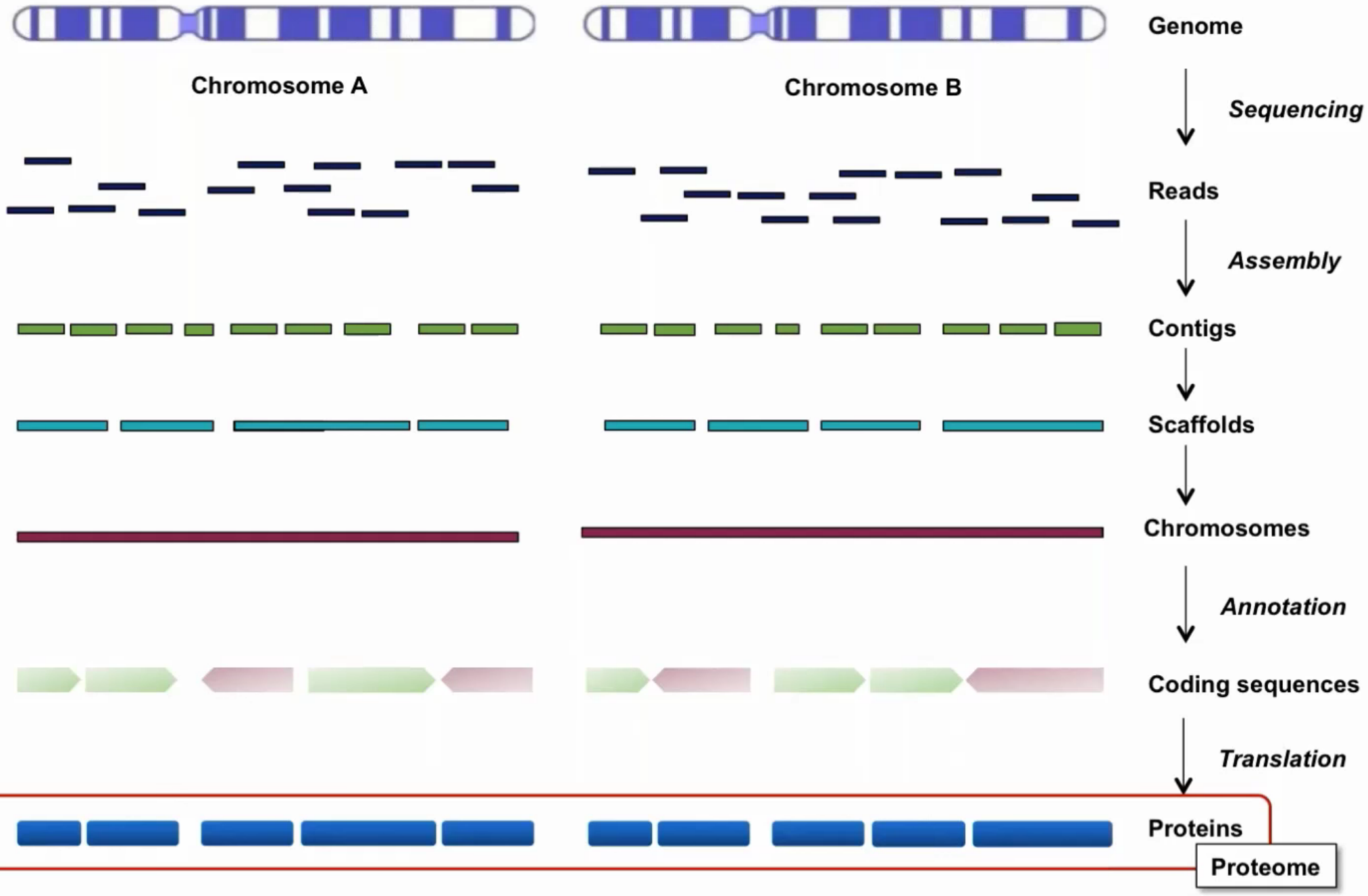
Protein existence (PE):	entries	%
1: Evidence at protein level	1436	16.6%
2: Evidence at transcript level	57673	10.5%
3: Inferred from homology	387609	70.5%
4: Predicted	11444	2.1%
5: Uncertain	1954	0.4%

UniProtKB/TrEMBL

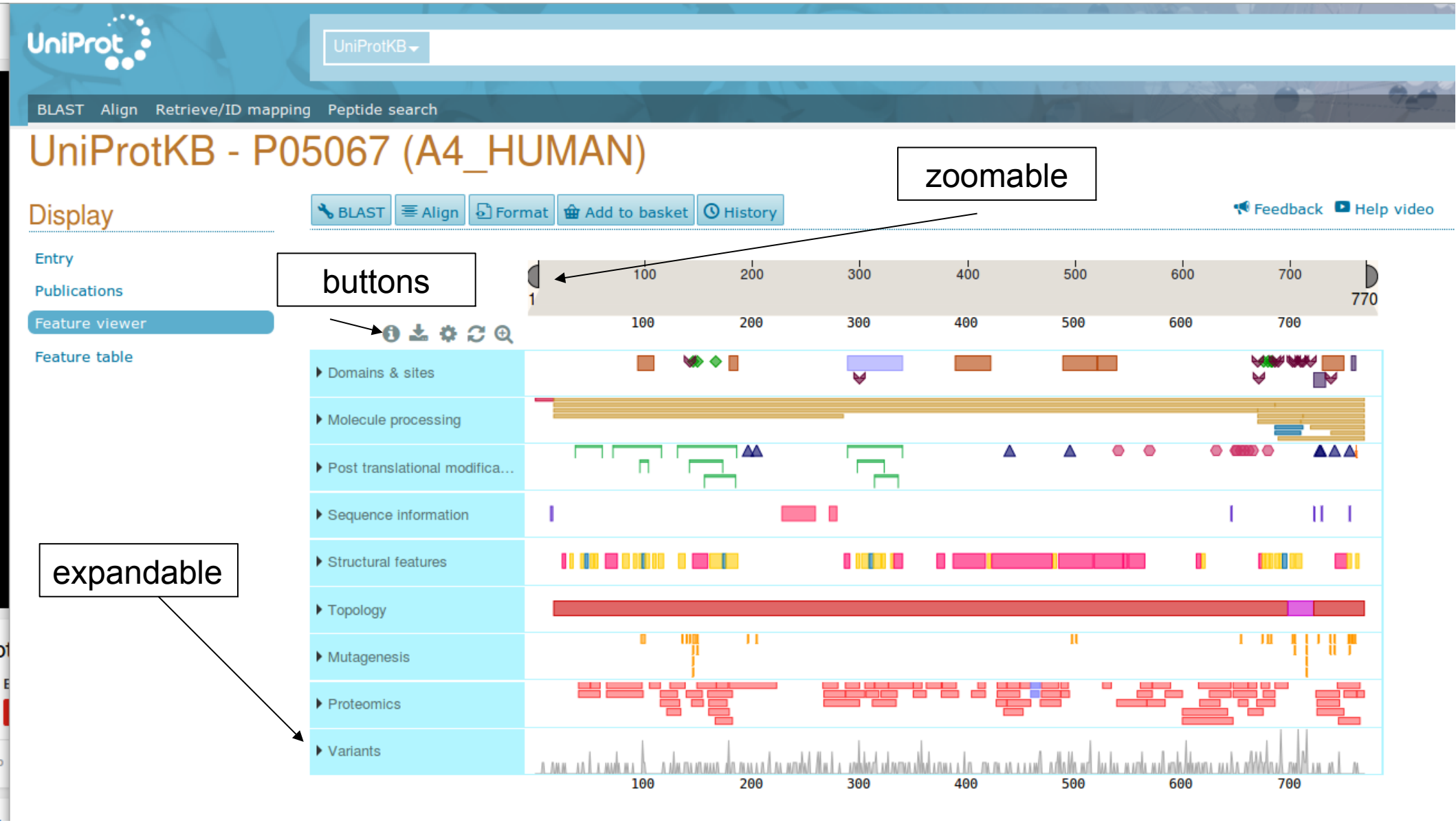
- Translations of CDS in EMBL/GenBank/DDBJ
- Automatic annotation
- Contains 54247468 entries

Protein existence (PE):	entries	%
1: Evidence at protein level	121173	0.22%
2: Evidence at transcript level	992520	1.80%
3: Inferred from homology	11944683	21.61%
4: Predicted	42212303	76.37%
5: Uncertain	0	0.00%

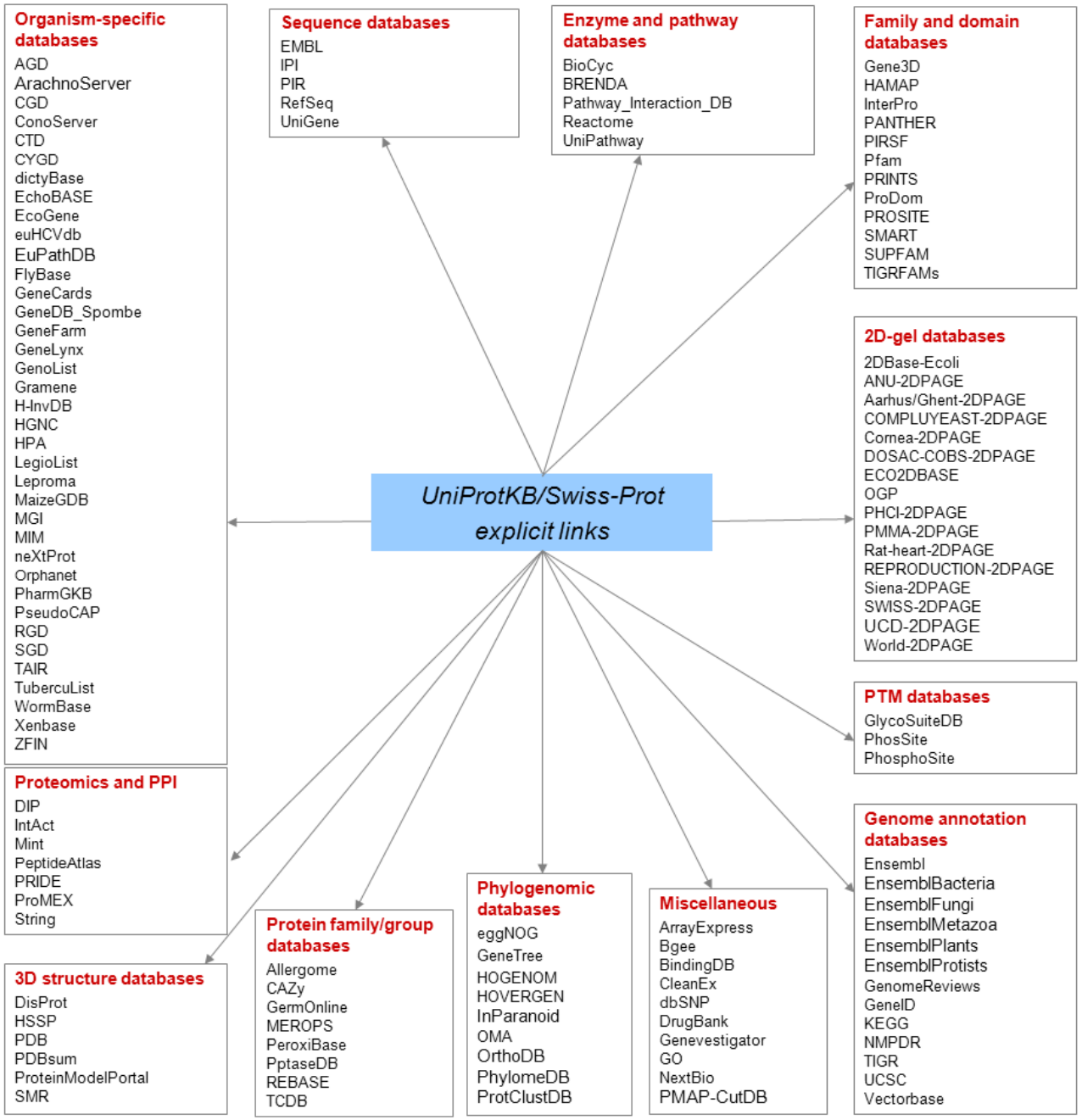
What are proteomes?



Feature viewer



Cross-references in UniProt



Function of proteins

What do we mean by function?
- could mean different things
- many levels of granularity
- functional categories are somewhat artificial
- ambiguities in naming

The same name can be used to describe different concepts, e.g:

- Glucose synthesis
- Glucose biosynthesis
- Glucose formation
- Glucose anabolism
- Gluconeogenesis

All refer to the process of making glucose
Makes it difficult to compare the information

Solution: use Ontologies and Data Standards, Controlled vocabularies

Ontologies

An ontology is a formal specification of terms and relationships between them – widely used in biology and boinformatics (e.g. taxonomy)

- The relationships are important and represented as graphs
- Ontology terms should have definitions
- Ontologies are machine-readable
- They are needed for ordering and comparing large data sets

Gene Ontology (GO)

- http://www.geneontology.org

- Many annotation systems are organism-specific or different levels of granularity

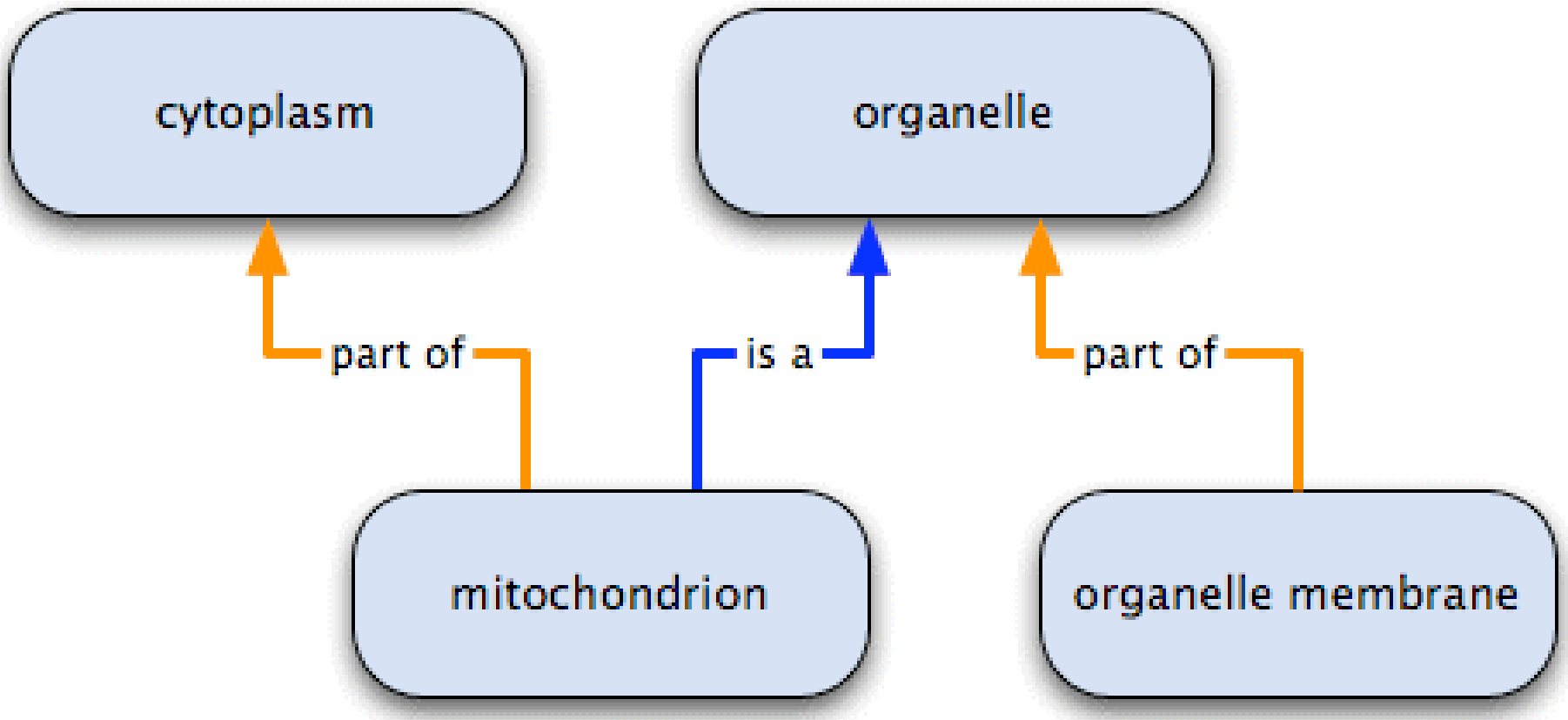
• GO introduced standard vocabulary first used for mouse, fly and yeast, but now generic

• Three ontologies

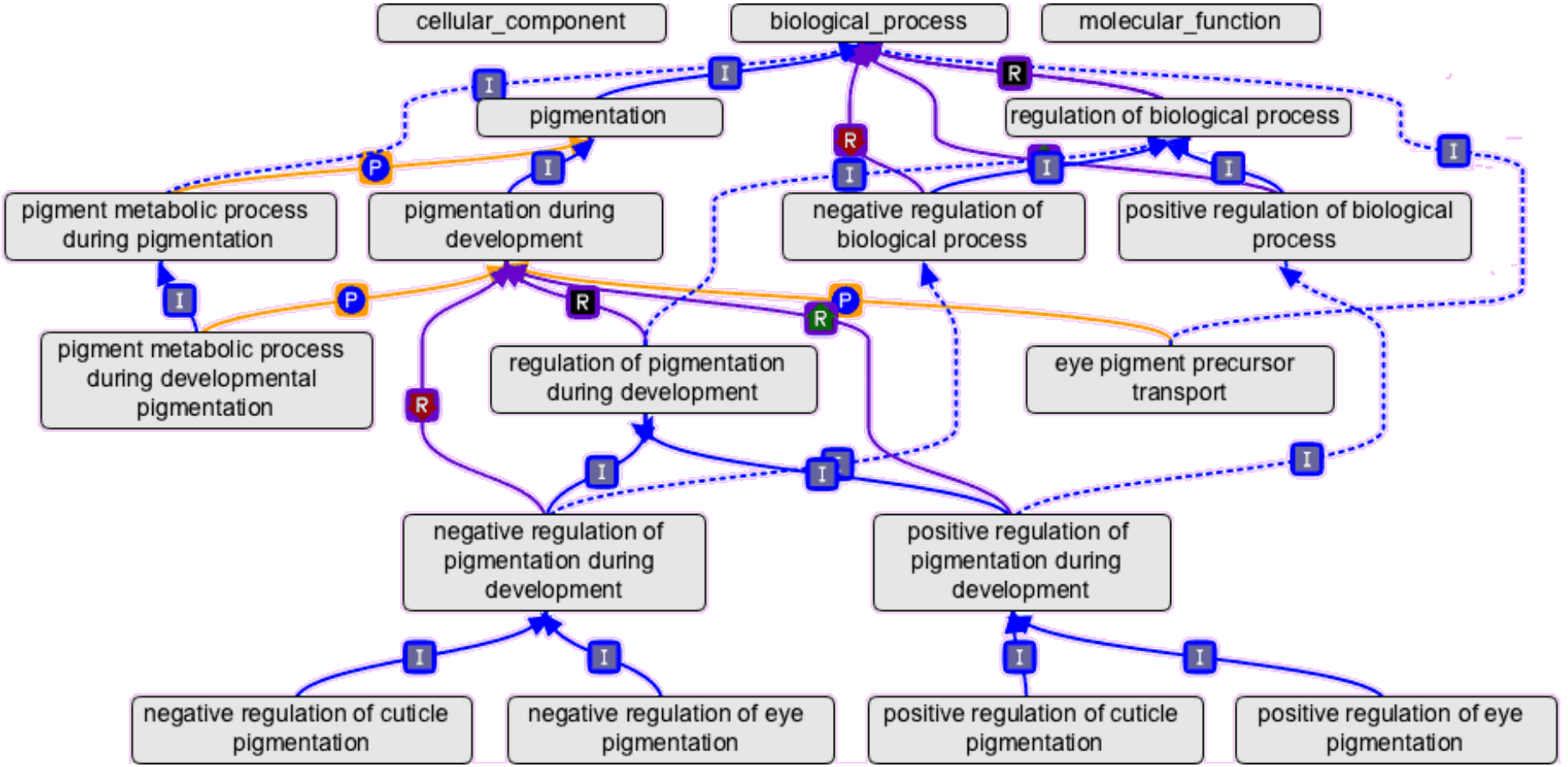
GO ontology

- **Molecular function**: tasks performed by gene product
  - –e.g. G-protein coupled receptor
- **Biological process**: broad biological goals accomplished by one or more gene products
  - –e.g. G-protein signaling pathway
- **Cellular component**: part(s) of a cell of which a gene product is a component; includes extracellular environment of cells
  - –e.g nucleus, membrane etc.

GO hiearchy


cytoplasm
organelle
part of
is a
part of
mitochondrion
organelle membrane

GO hierarchy



How do gene products get GO terms?

- Electronic annotation:

– Through mappings to other biological entities and then automatic inference to proteins

- Manual annotation:

– Model organism databases

– Gene Ontology Annotation (GOA) project

- Evidence codes –attached to all GO annotations to show the source

GO- slim

- GO slims are cut-down versions of the GO ontologies
- GO slims can give a summary of the result
- GO slims may be specific to species or to particular areas of the ontologies
- GO provides a generic GO slim
- Used for enrichment calculations

Genome Browser: ENSEMBL

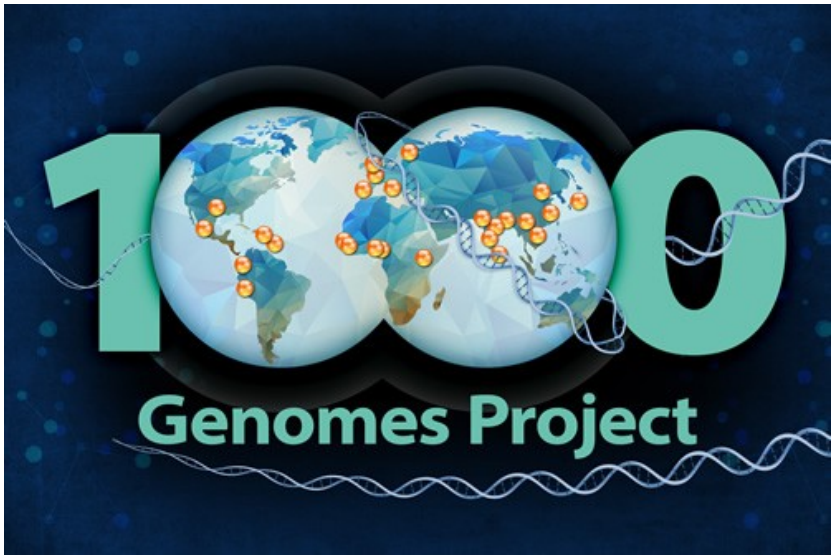
The Genome Reference Consortium (GRC) (1) released a new human genome assembly, GRCh38 (GCA_000001405.15), in December 2013.

Ensembl processes large-scale genomic data for chordate and model organisms

Genes and transcripts are annotated by aligning protein and mRNA sequences to the genomic sequence

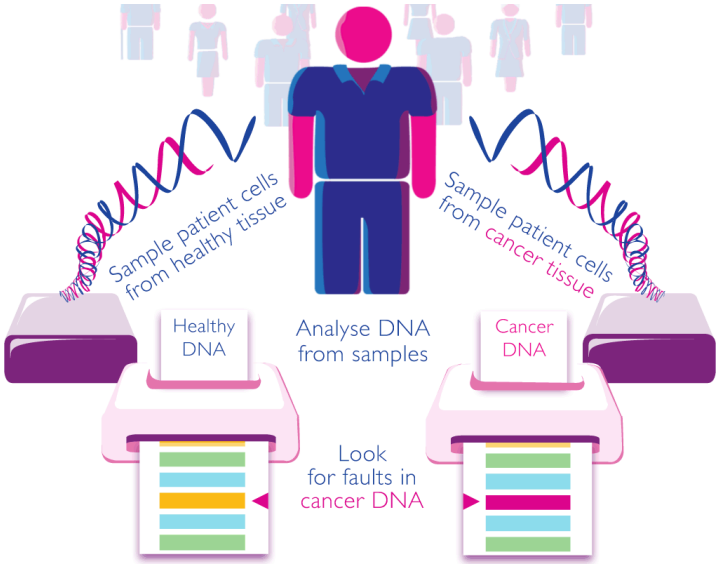
Genome Variations

Polymorphisms



(Common) polymorphisms:
Present in 1% in population

Cancer Genome Projects



Passenger and driver mutations

Visualization of cancer data

COSMIC

http://cancer.sanger.ac.uk/cosmic/gene/analysis?ln=TP53

CbioPortal (TCGA)

http://www.cbioportal.org/

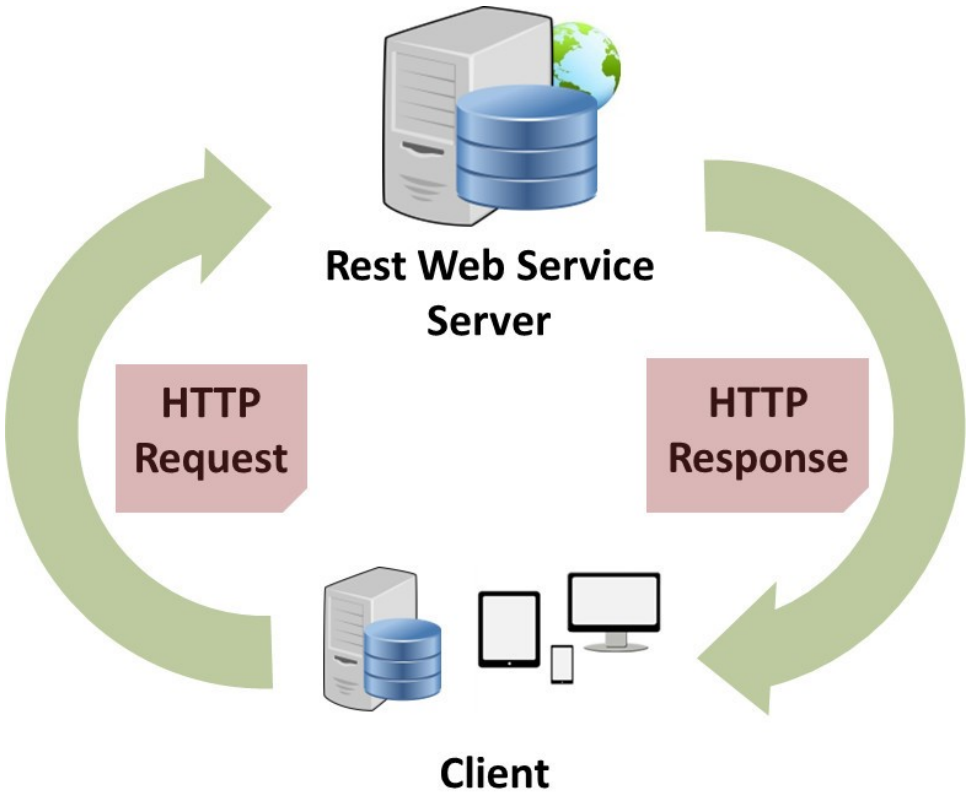
ICGC

https://dcc.icgc.org/genes/ENSG00000141510

Memphis (pediatric cancer)

https://pecan.stjude.org/#/proteinpaint/TP53

REST interface



Easier way of providing interoperability between computer systems through web services.

– The data can be requested with simple HTTP requests (in the URL)

– returned in a variety of programatic and bioinformatical relevant formats such as JSON, XML, TXT and FASTA.

– reproducible, scalable, powerful

Uniprot, PDB, ELM …