SERVERS

- **NCBI** (National Centre for Biotechnology Information)
  http://www.ncbi.nlm.nih.gov

- **SIB** (Swiss Institute of Bioinformatics)
  https://www.sib.swiss/

- **EBI-EMBL** (European Bioinformatics Institute)
  http://www.ebi.ac.uk

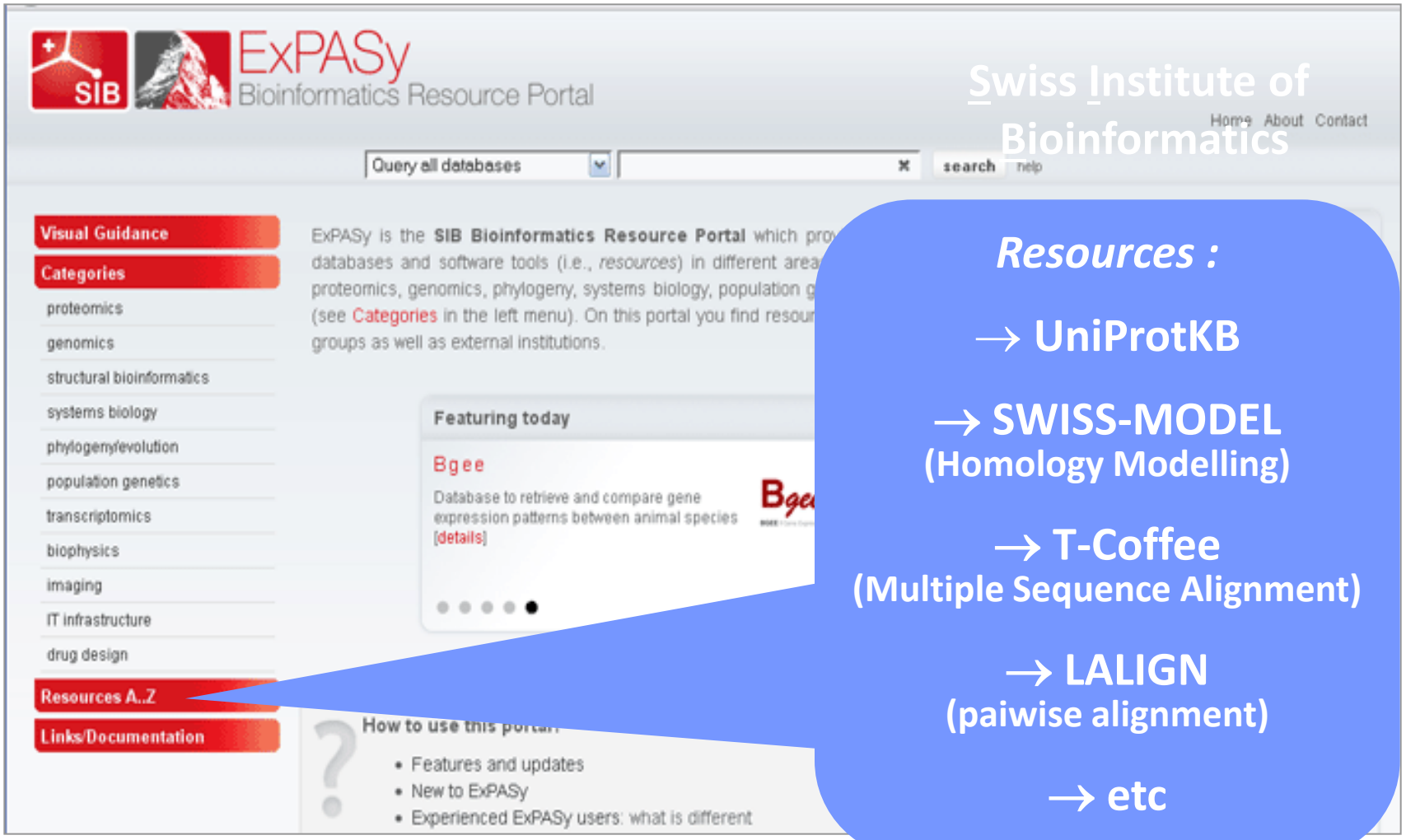
SIB (Swiss Intitute of Bioinformatics)

The SIB central administration is hosted in the Génopode Building of the University of Lausanne (Switzerland)

https://www.sib.swiss/

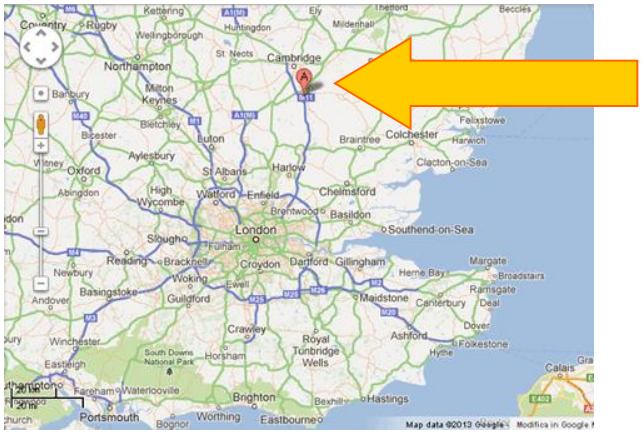
Expasy

http://www.expasy.org



European Bioinformatics Institute www.ebi.ac.uk

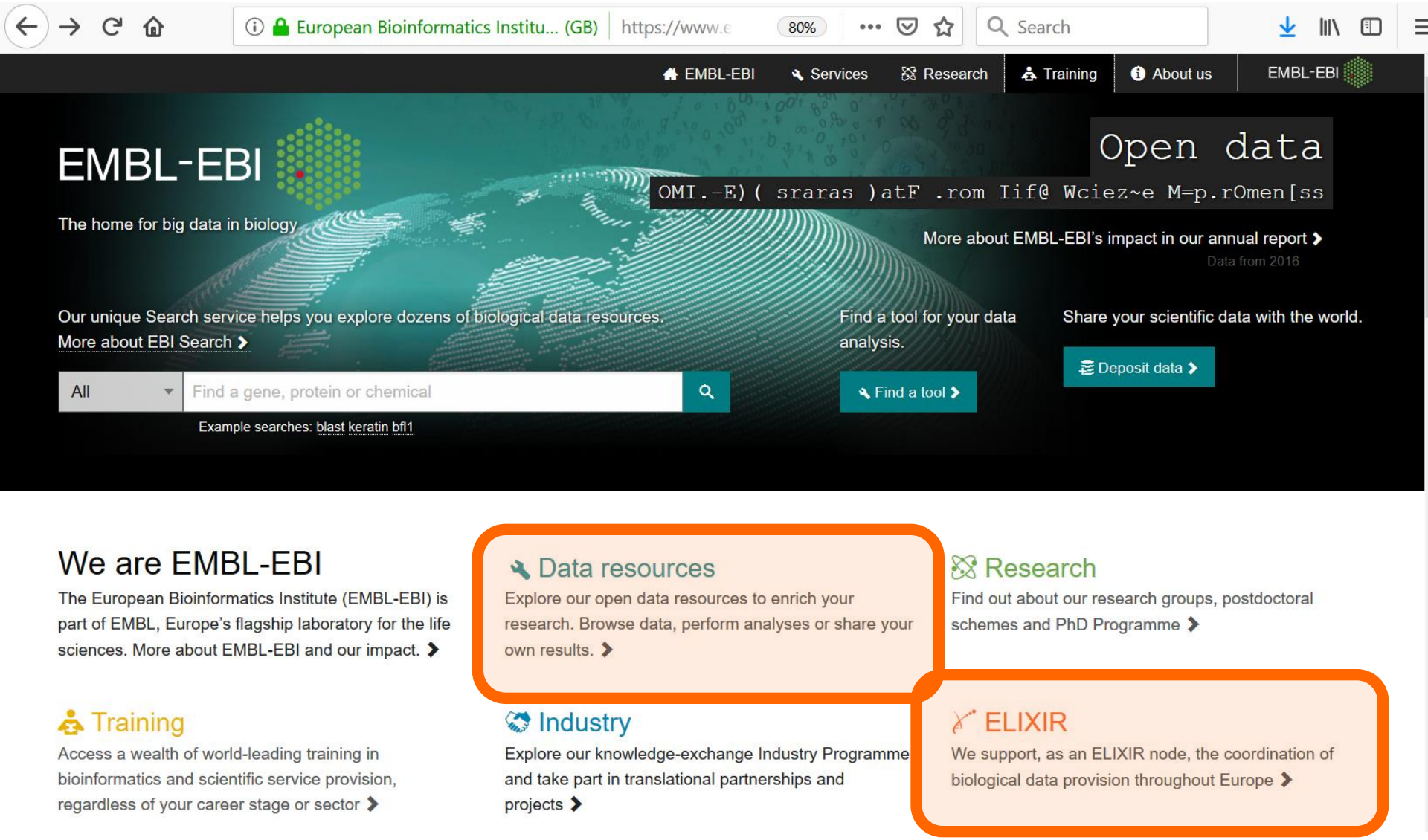
Branch of the EMBL, started in 1980 in Heidelberg.
Since 1995, at the Wellcome Trust Genome Campus at Hinxton



Mission (from the EBI website):

- To provide freely available **data and bioinformatics services** to all facets of the scientific community.
- To contribute to the advancement of biology through basic investigator-driven **research in bioinformatics**.
- To provide advanced bioinformatics **training to scientists** at all levels, from PhD students to independent investigators.
- To help disseminate cutting-edge technologies to **industry**.

EBI-EMBL http://www.ebi.ac.uk



Databases at EBI

UniProt

A comprehensive resource for protein sequence and functional annotation.

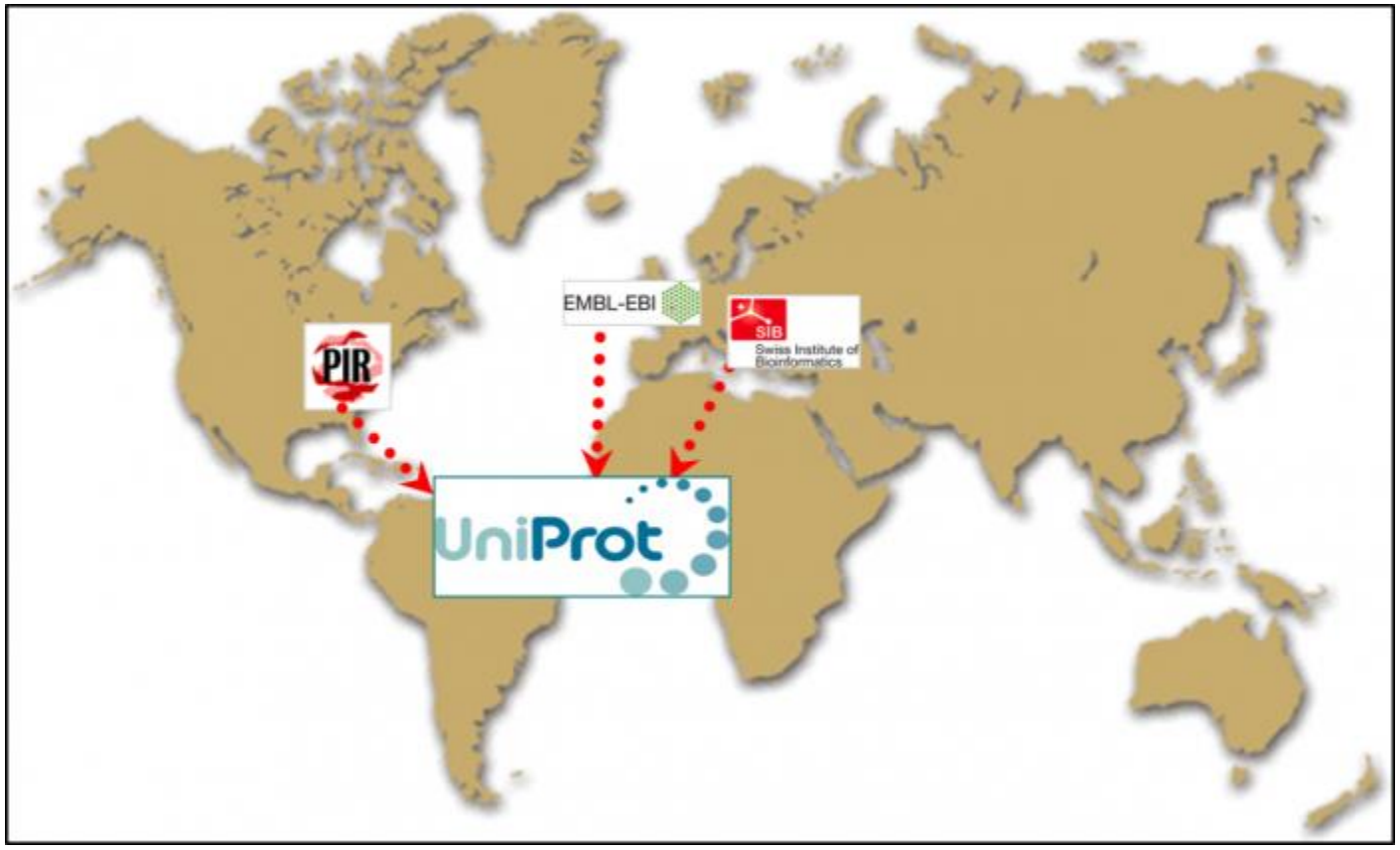
Ensembl

Genome browser, API and database, providing access to reference genome annotation.

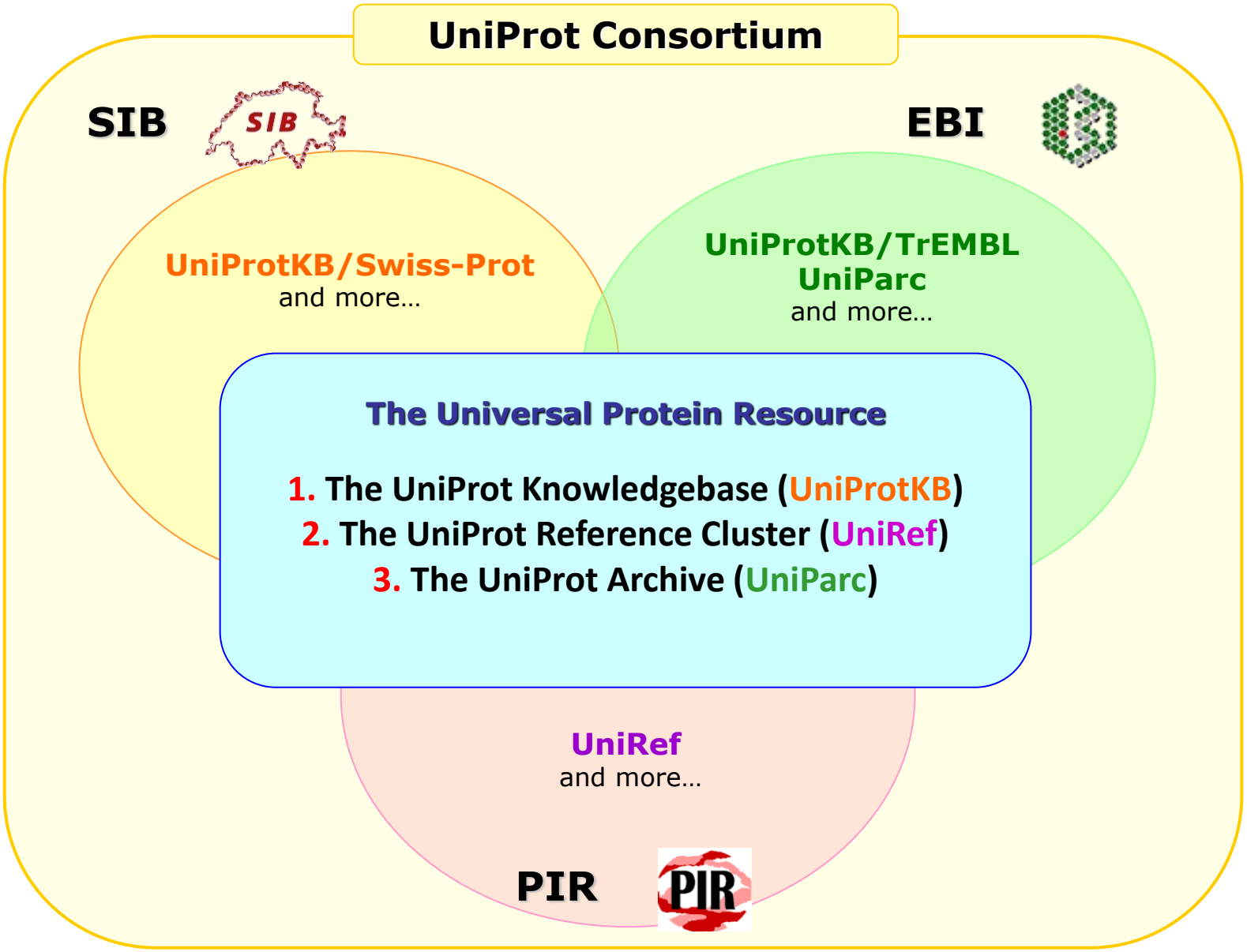
PDBe

The European resource for the collection, organisation and dissemination of 3D structural data (from PDB and EMDB).

Who produces UniProt ?



The UniProt Consortium



Nucleic Acids Research, 2004, Vol. 32, Database issue **D115–D119**
DOI: 10.1093/nar/gkh131

UniProt: the Universal Protein knowledgebase

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The EMBL Outstation—European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SD, UK, [1]Swiss Institute of Bioinformatics, Centre Medical Universitaire, 1 rue Michel Servet, 1211 Geneva 4, Switzerland, [2]Department of Biochemistry and Molecular Biology and [3]National Biomedical Research Foundation, Georgetown University Medical Center, 3900 Reservoir Road, NW, Box 571414, Washington, DC 20057-1414, USA

Received August 25, 2003; Revised and Accepted October 27, 2003

ABSTRACT

To provide the scientific community with a single, centralized, authoritative resource for protein sequences and functional information, the Swiss-Prot, TrEMBL and PIR protein database activities have united to form the Universal Protein Knowledgebase (UniProt) consortium. Our mission is to provide a comprehensive, fully classified, richly and accurately annotated protein sequence knowledgebase, with extensive cross-references and query interfaces. The central database will have two sections, corresponding to the familiar Swiss-Prot (fully manually curated entries) and TrEMBL (enriched with automated classification, annotation and extensive cross-references). For convenient sequence searches, UniProt also provides several

The primary mission of the consortium is to support biological research by maintaining a high-quality database that serves as a stable, comprehensive, fully classified, richly and accurately annotated protein sequence knowledgebase, with extensive cross-references and querying interfaces freely accessible to the scientific community. UniProt will build upon the solid foundations laid by the consortium members over many years.

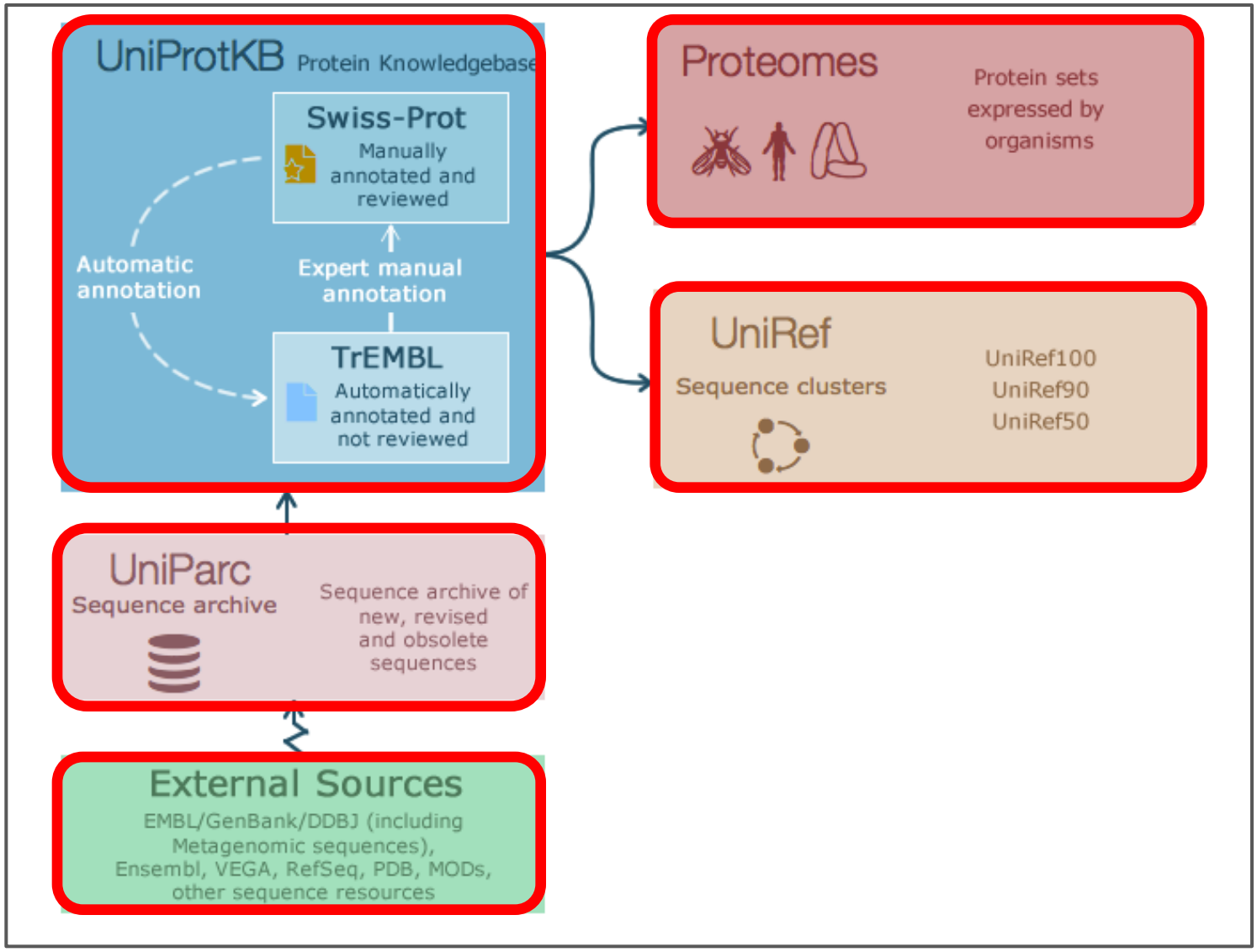
The UniProt databases consist of three database layers:

(i) The UniProt Archive (UniParc) provides a stable, comprehensive, non-redundant sequence collection by storing the complete body of publicly available protein sequence data.

(ii) The UniProt Knowledgebase (UniProt) provides the central database of protein sequences with accurate, consistent and rich sequence and functional annotation.

(iii) The UniProt NREF databases (UniRef) provide non-redundant data collections based on the UniProt knowledgebase in order to obtain complete coverage of sequence space at several resolutions.

Sources and flow of data for UniProt databases

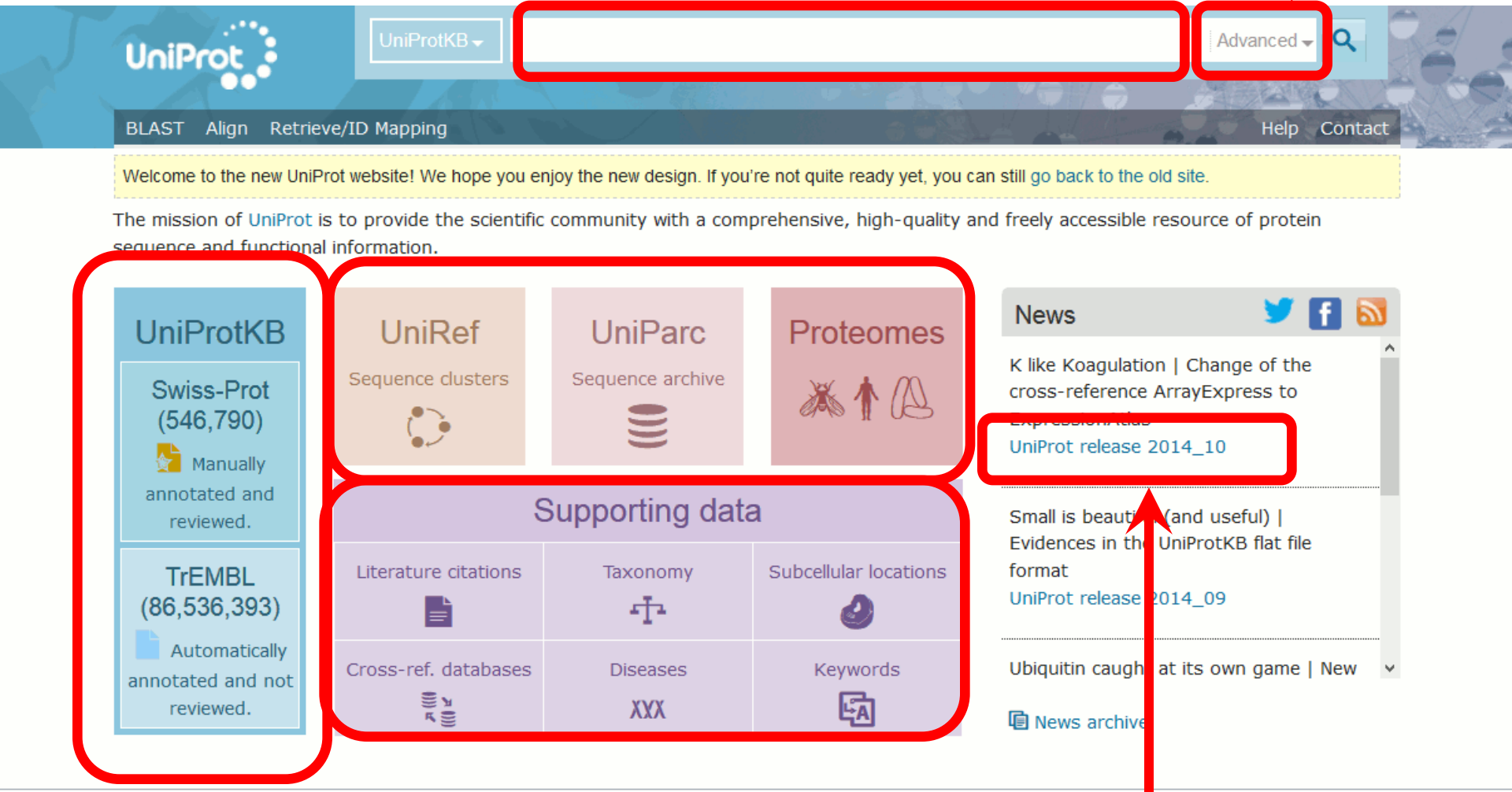


UniProt

http://www.uniprot.org/

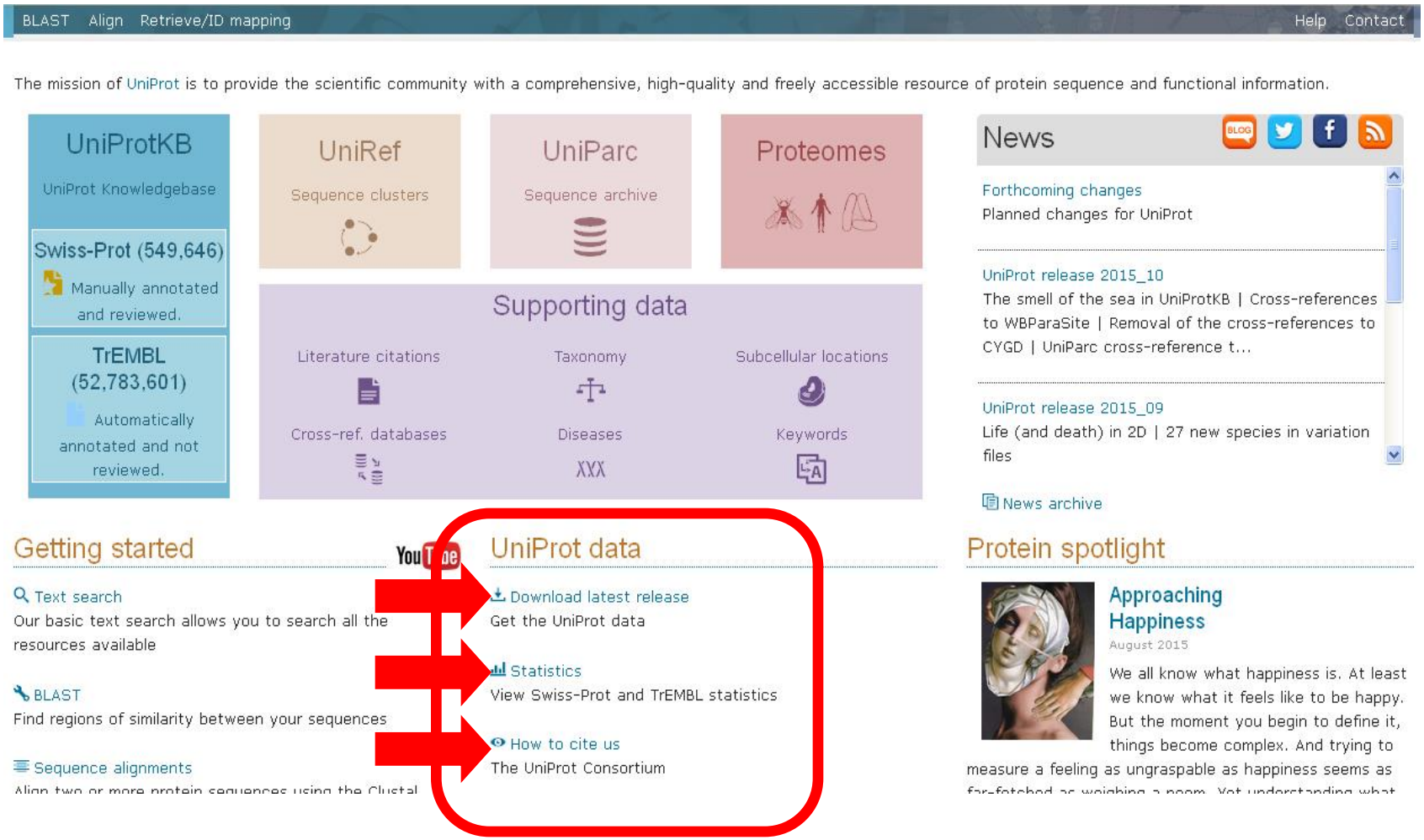
search bar

advanced

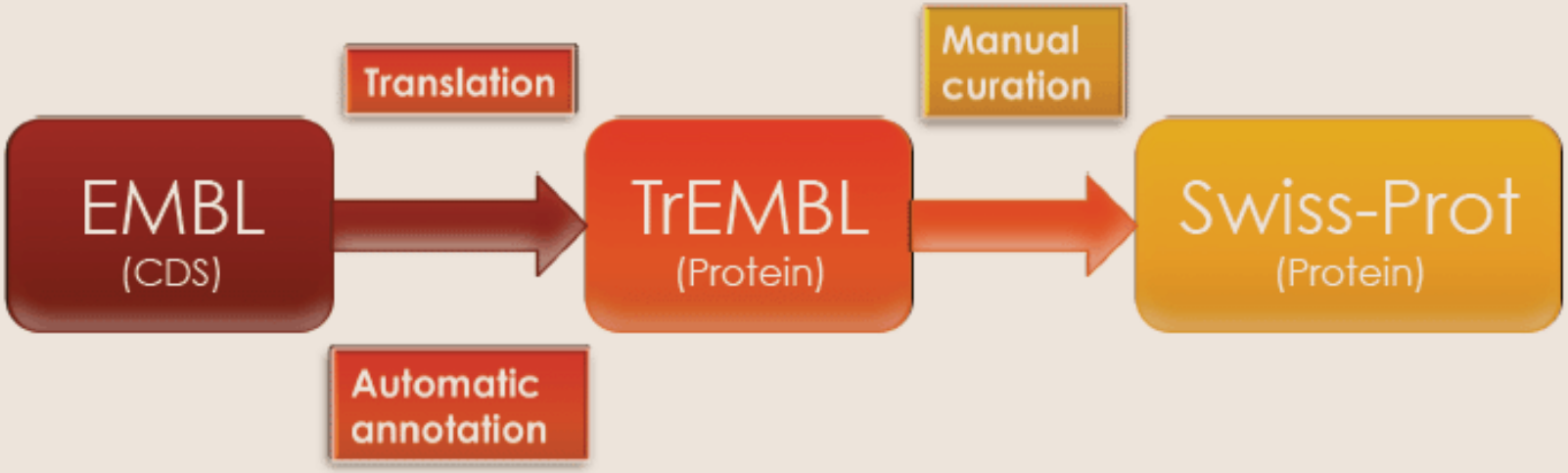


date of last release

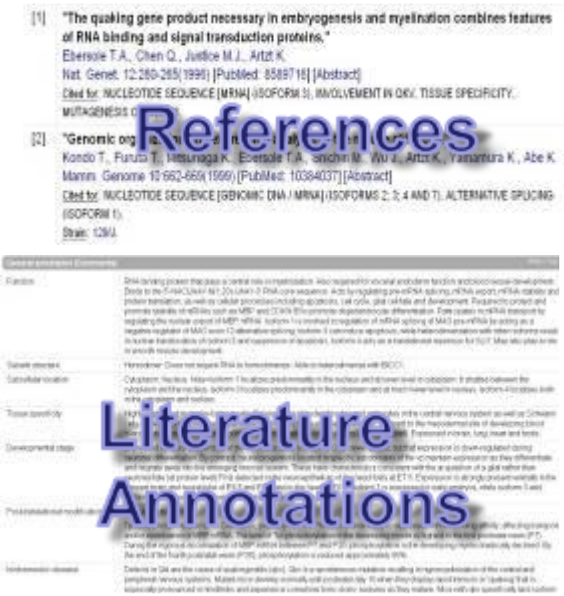
UniProt data

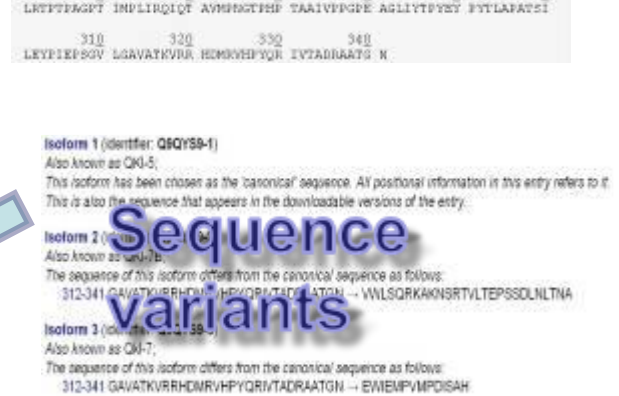


Data Flow from EMBL DNA sequences to Swiss-Prot

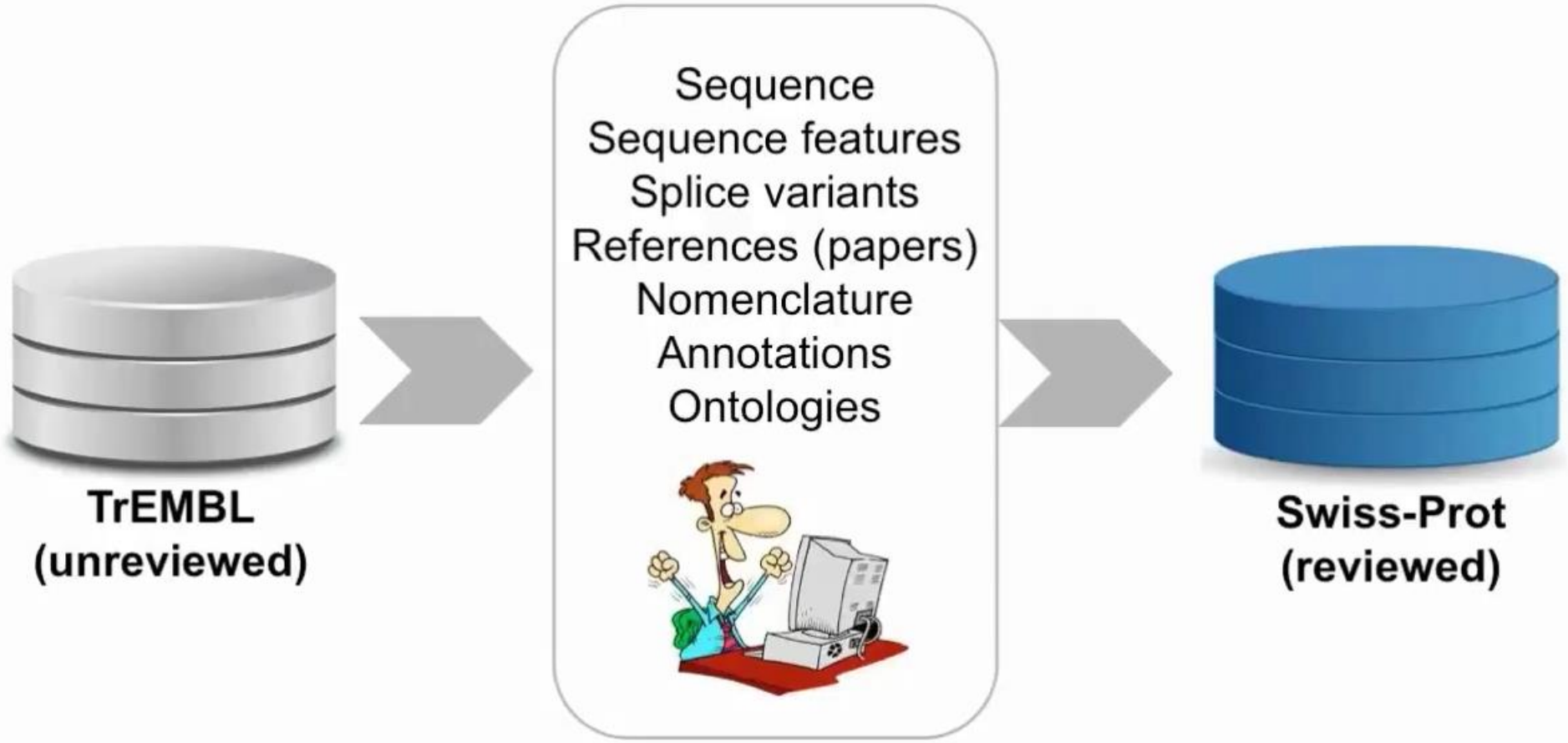


Information Added to a UniProt/Swiss-Prot entry





Manual Curation of UniProtKB Entries



Sequence Curation

Discrepancies between sequence reports are identified, and the underlying causes of the sequence differences such as:

- alternative splicing
- natural variations
- frameshifts
- incorrect initiation sites
- incorrect exon boundaries
- unidentified conflicts
- erroneous gene prediction

are documented.

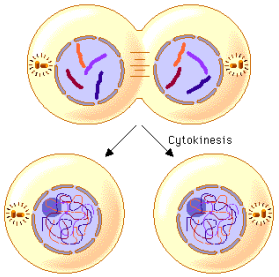
Comparison with homologous sequences is also used to identify additional sequence errors and their causes.

These steps ensure that the sequence described for each protein in UniProtKB/Swiss-Prot is as complete and correct as possible.

Gene Ontology (GO)

1. Biological Process

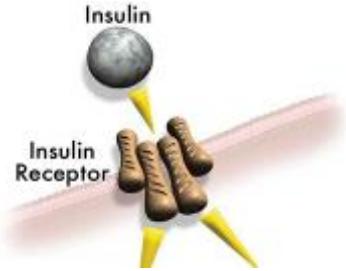
A commonly recognized series of events



- cell division
- Mitosis
- organelle fission

2. Molecular Function

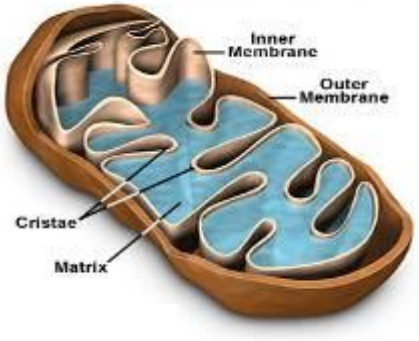
An elemental activity or task or job



- protein kinase activity
- insulin binding
- insulin receptor activity

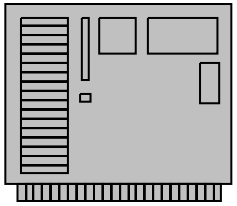
3. Cellular Component

Where a gene product is located



- mitochondrion
- mitochondrial matrix
- mitochondrial membrane

The Two Sides of UniProtKB



UniProtKB/**TrEMBL**

Redundant
(1 entry per translated ENA entry),
computationlly analyzed,
automatically annotated.
Unreviewed

e.g. Accession Q9N0H9
Entry Name Q9N0H9_EQUAS

UniProtKB/**Swiss-Prot**

Non-redundant
(1 entry per protein),
curator-evaluated analysis,
high-quality manual annotation.
Reviewed

e.g. Accession P38398
Entry Name BRCA1_HUMAN

UniProt (1) – Entry Name

http://www.uniprot.org/help/entry_name

Find out which ones of the following 5 entries are unreviewed:

1) Q84J55 14331_ORYSJ
2) Q0DV28 ARK1_ORYSJ
3) Q5Z8U4 Q5Z8U4_ORYSJ
4) P00986 VKT2_NAJNI
5) Q8WA21 Q8WA21_NAJNI

Uniprot KnowledgeBase Introduction (video)

https://www.youtube.com/watch?v=ado1r8IDm3U

Reading a SwissProt or trEMBL Entry

- General information about the Entry
  (primary AC, Entry Name, History, annotation score.)
- Name and Origin of the Protein
  (Protein Name, Synonymous, Gene Name, Source, Taxonomy, EC Number.)
- Function
  (Protein Length, Binding Sites, GO terms, Keywords, EC Number, Subunits.)
- Subcell. location, Pathology, PTM, Expression, Interactions.
- Structure, Family and Domains, Sequence.
- Cross-References, Publications, Entry Information, Similar Proteins
  (Sequence databases, Structure databases, link to UniRef.)

UniProt (2) – downloads

A. Download, as an uncompressed Excel table, all entries from *Saccharomyces cerevisiae* (Baker's yeast) :

1) which are reviewed;
2) whose function is "DNA binding";

showing for each entry the content of the following fields:

1) Accession Number;
2) Entry Name;
3) Protein Name;
4) Gene Name;
5) Length;
6) Evidence for existence;
7) GO terms for "biological process", "molecular function" "cellular component";
8) DNA binding.

B. Map the UniProtKB IDs of all found entries to their EMBL/GenBank/DDBJ IDs.

UniProt (3) – Feature viewer

Go to the entry with AC number P06858.

1) Switch the «Display» from «entry» to «Feature viewer».

2) In «Domains & sites», click on the dot representing the active site residue 183.

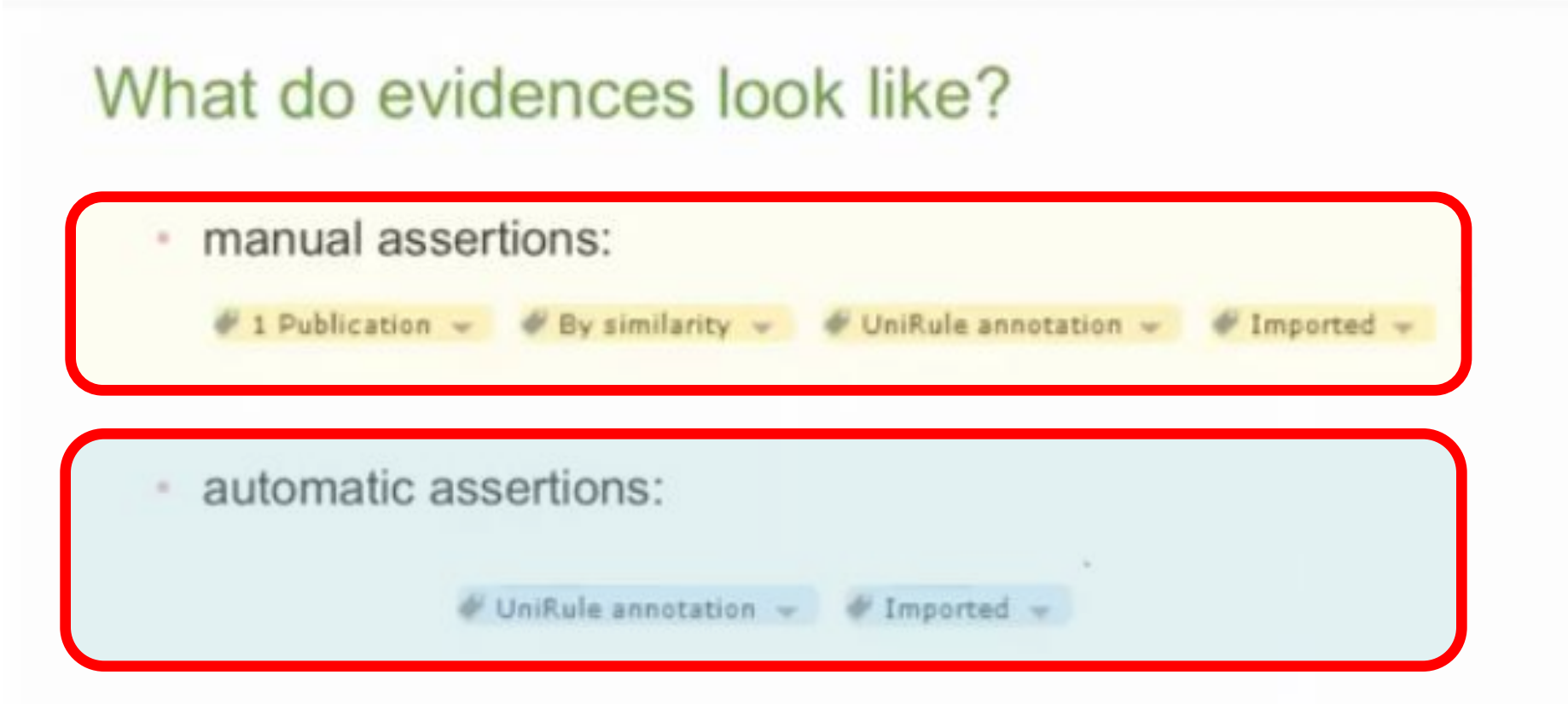
3) Using the ruler on top of the view, zoom in to that residue, with a window of about 50 residues. In the «Variants» section, find out which variations are known for that residue. Are they pathogenic? Which are the cross-references for each variant?

4) Find the same information with the «Display» switched back to «entry».

UniProt (4) – From diseases to protein variants

⇒ **Questionnaire on UniProt, #1**

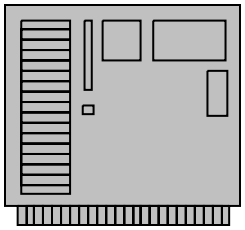
Evidence tags



TrEMBL – Automatic Annotation

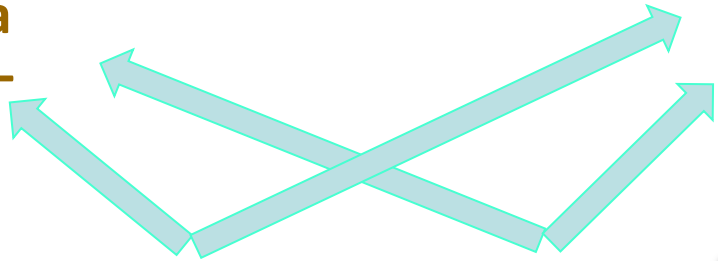
Automatic Annotation

UniProtKB employs two prediction programs which are referred to as UniRule and SAAS.



SAAS, Statistical Automatic Annotation System, generates a new set of decision-trees with every UniProtKB release using data-mining.

UniRule maintains a set of manually established annotation rules.



InterPro is an EBI database that collates domain signatures and defines protein family membership.

UniProt (5) – example of UniRule

1) Go to the entry Q02PG5. The recommended name for this protein is «Glyceraldehyde-3-phosphate dehydrogenase-like protein». Which is the code of the UniRule rule according to which this annotation has been issued?

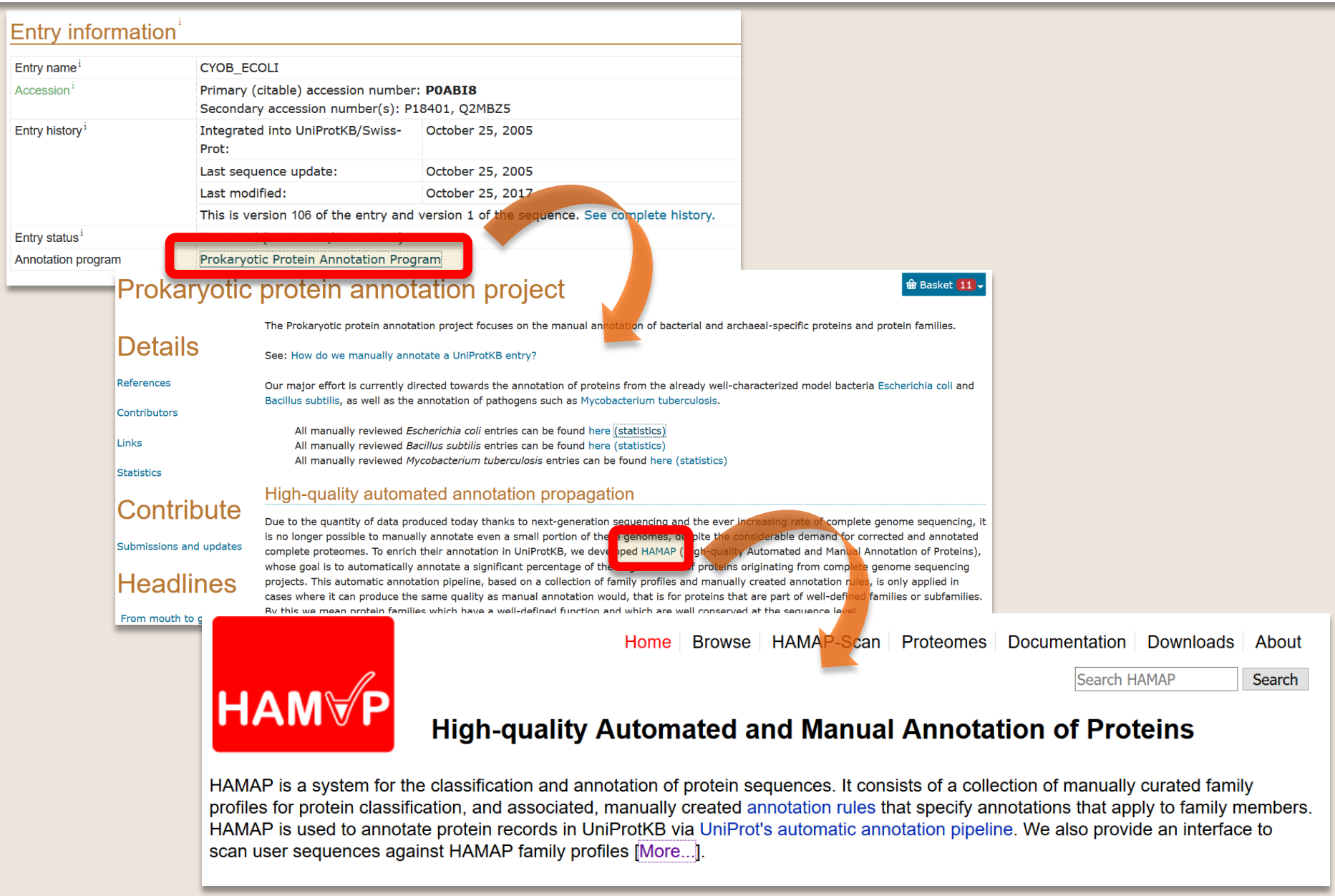
2) Which are the common conditions required to issue such annotation?

3) How many rules are there in UniRule?

UniProt (6) – example of SAAS

1) Go to the entry Q87644. The catalytic activity has been annotated with «ATP + H_2O = ADP + phosphate». Which is the code of the SAAS rule according to which this annotation has been issued?
2) Which are the common conditions required to issue such annotation?
3) How many proteins are annotated with this rule in the whole database?

HAMAP: Automatic Annotation Programs



HAMAP

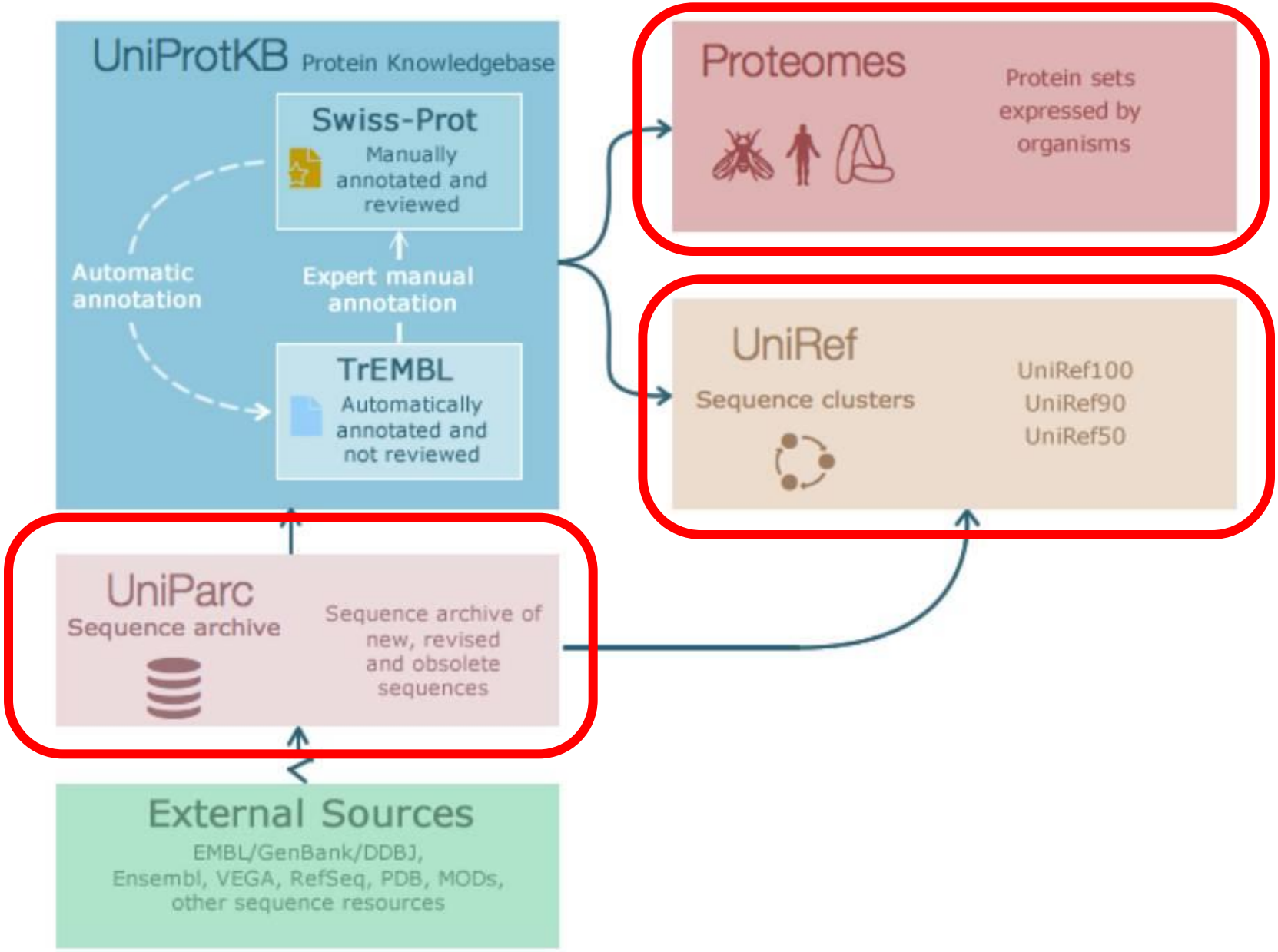
HAMAP is based on a collection of expert curated protein family profiles, which are used to determine family membership of protein sequences, and annotation rules.

HAMAP rules permit the annotation of protein sequences to the same level of detail and quality as manually curated UniProtKB/Swiss-Prot records, annotating protein and gene names, function, catalytic activity, cofactors, subcellular location, protein–protein interactions, etc.

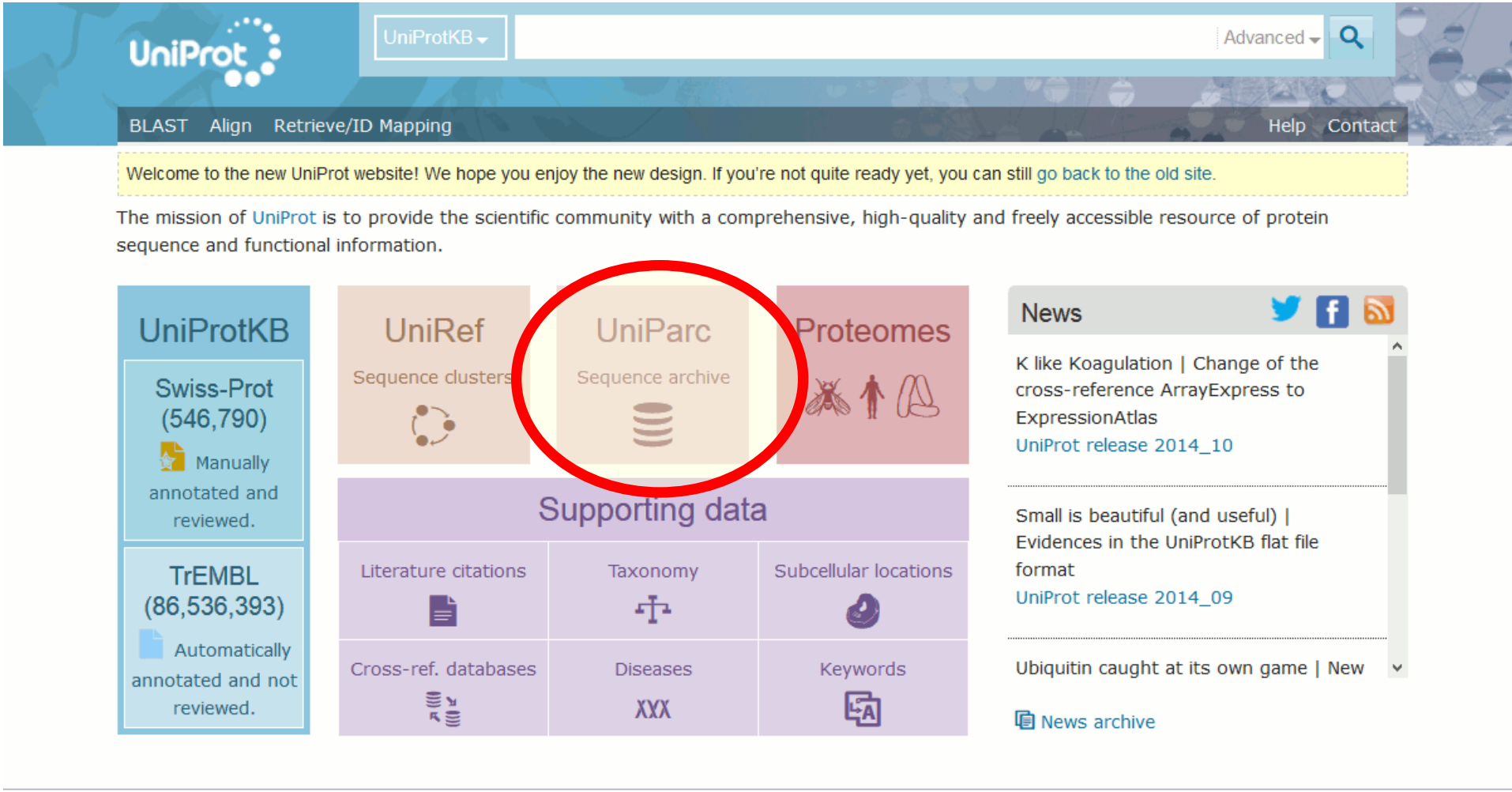
HAMAP rules also specify the conditions under which these annotations may be applied, such as a requirement for key functional residues (identified by structural or other experimental studies). Such conditions can reduce the incidence of erroneous annotation, particularly in large, functionally diverse families— errors that tend to persist in public sequence databases.

About UniProt

http://www.uniprot.org/help/about



UniParc


UniProt
UniProtKB
Advanced
BLAST
Align
Retrieve/ID Mapping
Help
Contact
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Manually annotated and reviewed.
TrEMBL (86,536,393)
Automatically annotated and not reviewed.
UniRef
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Sequence archive
Proteomes
Supporting data
Literature citations
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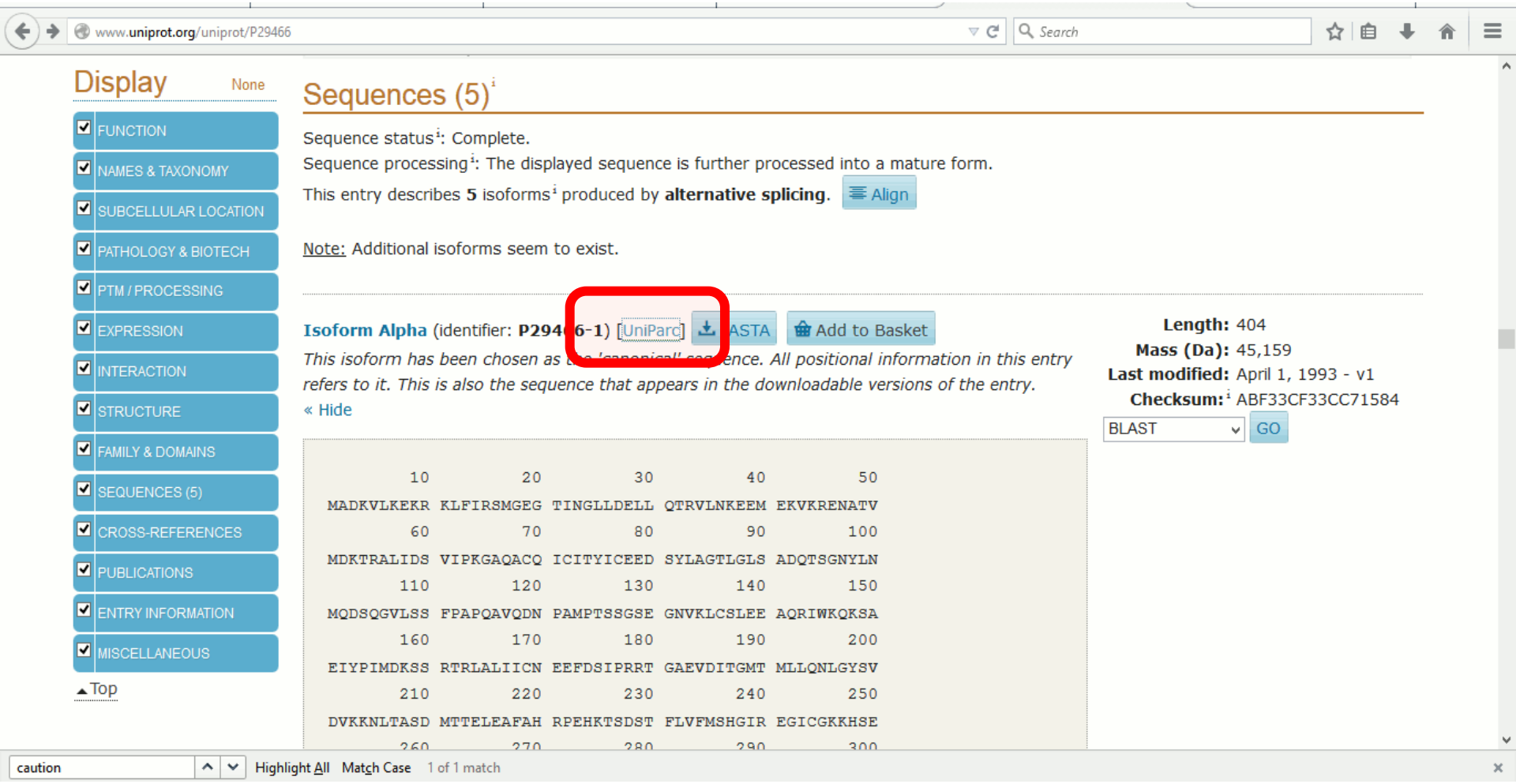
News archive

UniParc


www.uniprot.org/uniprot/P29466
Search
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FUNCTION
NAMES & TAXONOMY
SUBCELLULAR LOCATION
PATHOLOGY & BIOTECH
PTM / PROCESSING
EXPRESSION
INTERACTION
STRUCTURE
FAMILY & DOMAINS
SEQUENCES (5)
CROSS-REFERENCES
PUBLICATIONS
ENTRY INFORMATION
MISCELLANEOUS
Top
Sequences (5)
Sequence status: Complete.
Sequence processing: The displayed sequence is further processed into a mature form.
This entry describes 5 isoforms produced by alternative splicing.
Align
Note: Additional isoforms seem to exist.
Isoform Alpha (identifier: P294 6-1) [UniParc]
ASTA
Add to Basket
This isoform has been chosen as the 'canonical' sequence. All positional information in this entry refers to it. This is also the sequence that appears in the downloadable versions of the entry.
« Hide
10 20 30 40 50
MADKVLKEKR KLFIRSMGEG TINGLLDELL QTRVLNKEEM EKVKRENATV
60 70 80 90 100
MDKTRALIDS VIPKGAQACQ ICITYICEED SYLAGTLGLS ADQTSGNYLN
110 120 130 140 150
MQDSQGVLSS FPAPQAVQDN PAMPTSSGSE GNVKLCSLEE AQRIWKQKSA
160 170 180 190 200
EIYPIMDKSS RTRLALIICN EEFDSIPRRT GAEVDITGMT MLLQNLGYSV
210 220 230 240 250
DVKKNLTASD MTTELEAFAH RPEHKTSDST FLVFMSHGIR EGICGKKHSE
260 270 280 290 300
Length: 404
Mass (Da): 45,159
Last modified: April 1, 1993 - v1
Checksum: ABF33CF33CC71584
BLAST
GO
caution
Highlight All
Match Case
1 of 1 match

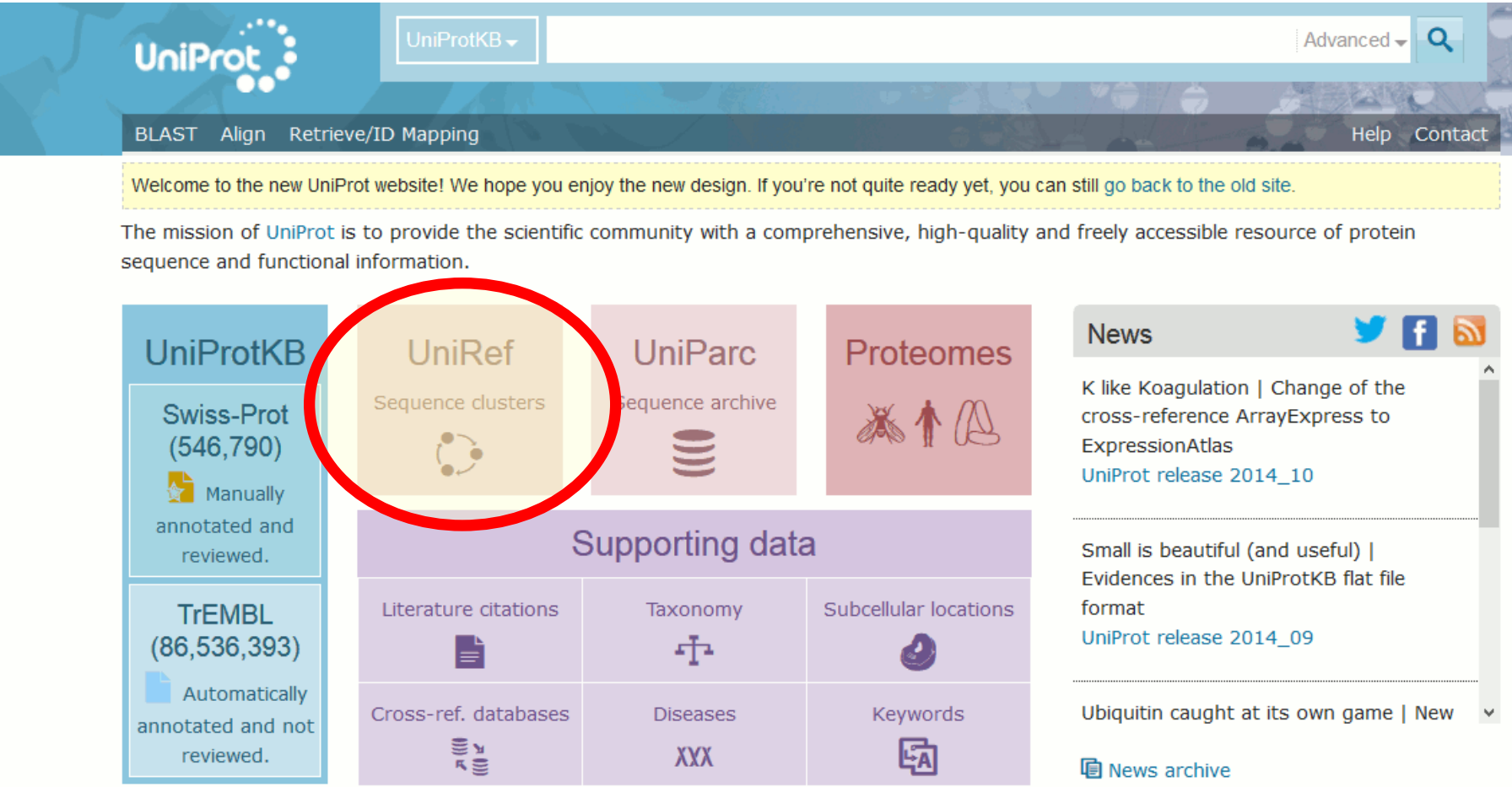
UniParc

UniParc is the most comprehensive publicy accessible **non-redundant** protein database.

UniParc records are **not annotated** because annotation is context-dependent: proteins with the same sequence can have different functions depending on species, tissue, developmental stage or other variables.

This **context-dependent information** is the scope of **UniProtKB**.

UniRef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UniProt release 2014_09
Ubiquitin caught at its own game | New
News archive

UniRef

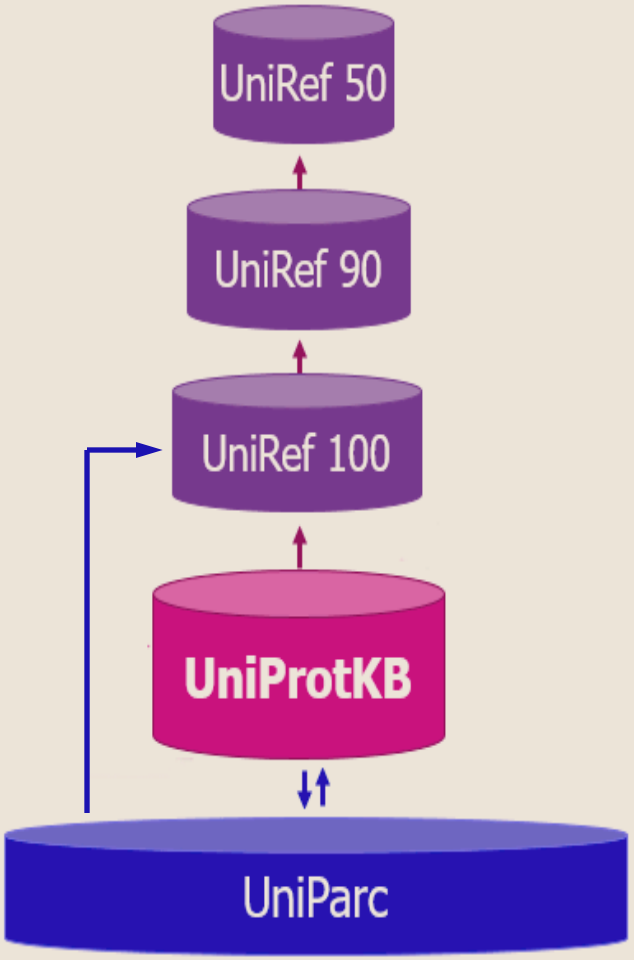
The UniProt Reference Clusters (UniRef) provide clustered sets of sequences from the UniProt Knowledgebase (including isoforms) and selected UniParc records. This hides redundant sequences and obtains complete coverage of the sequence space at three resolutions:

UniRef100 combines identical sequences and sub-fragments with 11 or more residues from any organism into a single UniRef entry.

UniRef90 is built by clustering UniRef100 sequences such that each cluster is composed of sequences that have at least 90% sequence identity to, *and 80% overlap with*, the longest sequence (seed).

UniRef50 is built by clustering UniRef90 seed sequences that have at least 50% sequence identity to, *and 80% overlap with*, the longest sequence (seed) in the cluster.

UniRef



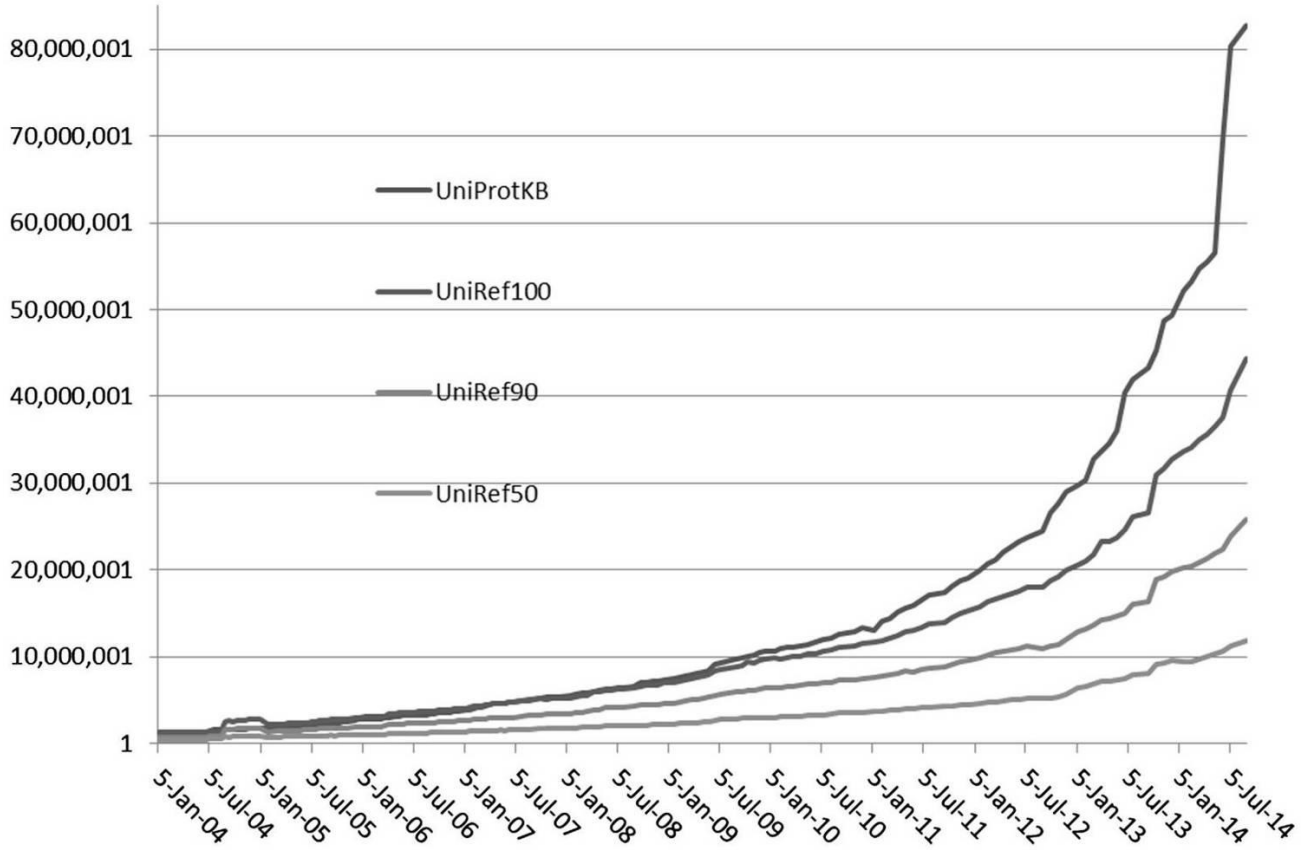
Database size reduction:

≈ 70% (UniRef90)

≈ 85% (UniRef50)

significantly faster sequence searches.

Growth of UniRef Databases and UniProt Knowledgebase



Baris E. Suzek et al. Bioinformatics 2015;31:926-932

UniRef50-based BLASTP searches are faster (6x), more concise (lists are 7x shorter), and overall more sensitive in the detection of remote similarities.

From *http://www.uniprot.org/help/uniref/*

The seed sequences are the longest members of the cluster.

However, the biologically relevant information (name, function, cross-references) is often available on other cluster members.

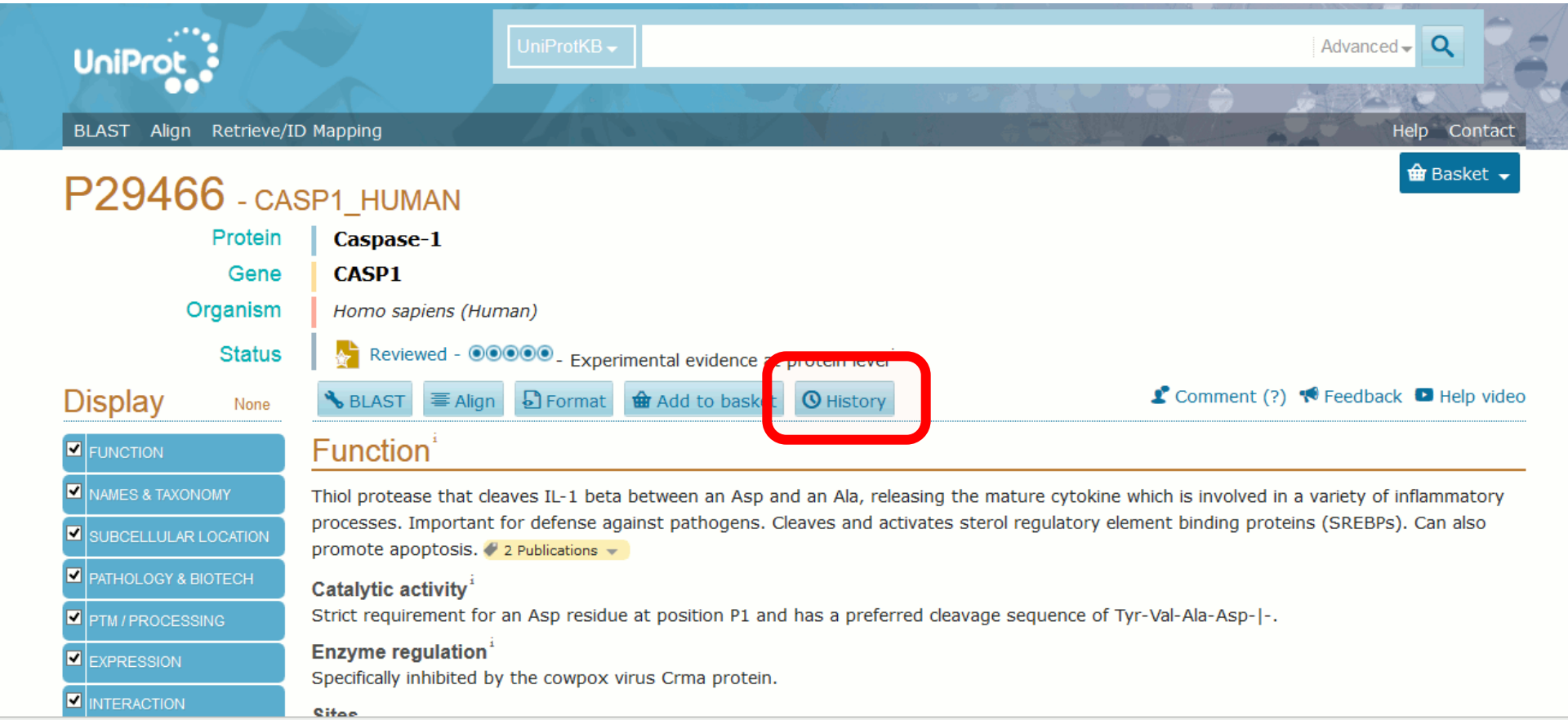
The biologically relevant representative for the cluster is chosen based on:

- ✔ quality of the entry: manually reviewed entries are preferred
- ✔ UniProtKB annotation score: higher are preferred
- ✔ organism: entries from reference proteomes and model organisms are preferred
- ✔ length of the sequence: longest sequence is preferred

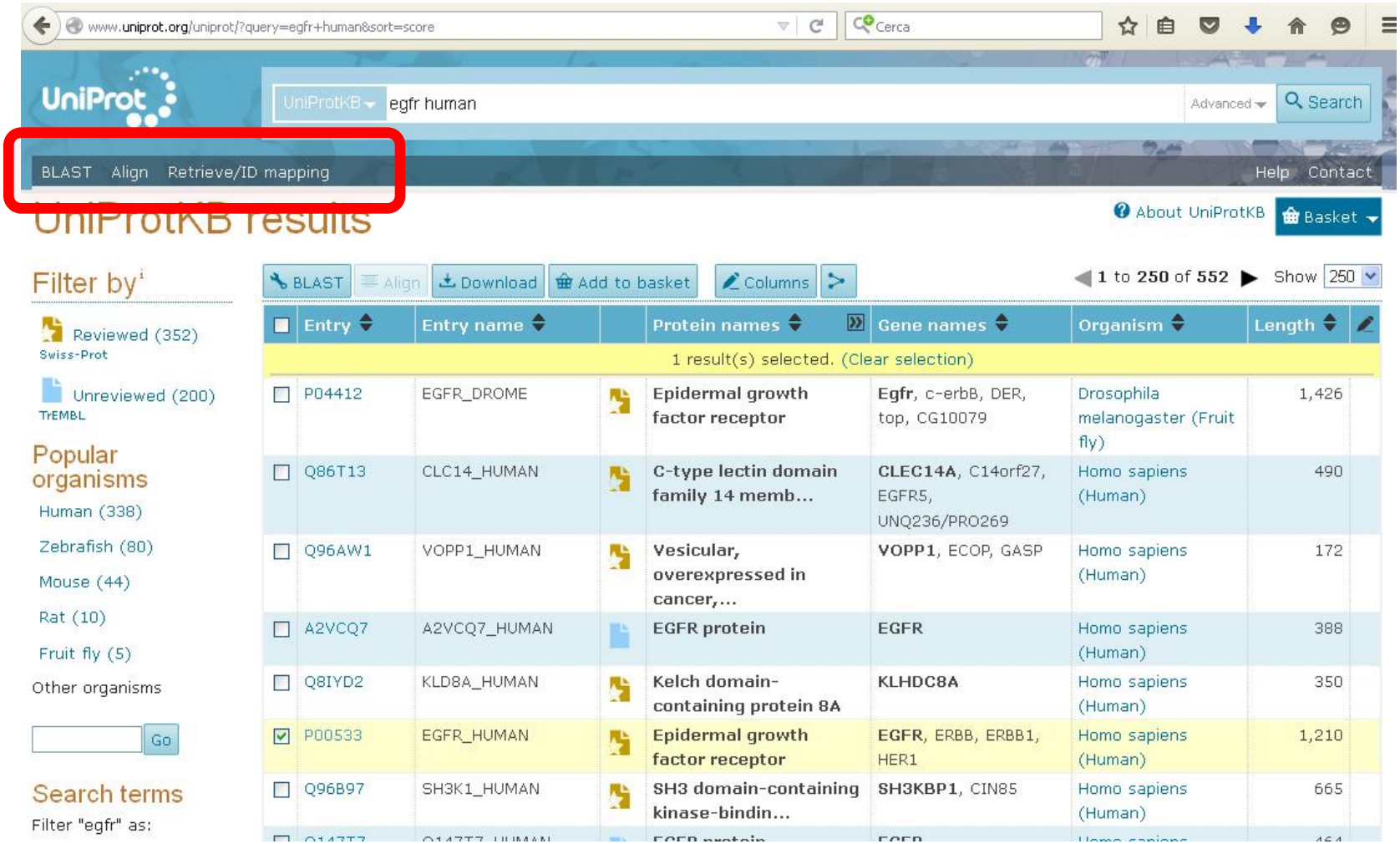
UniProt (8) – Searches

⇒ **Questionnaire on UniProt #2**

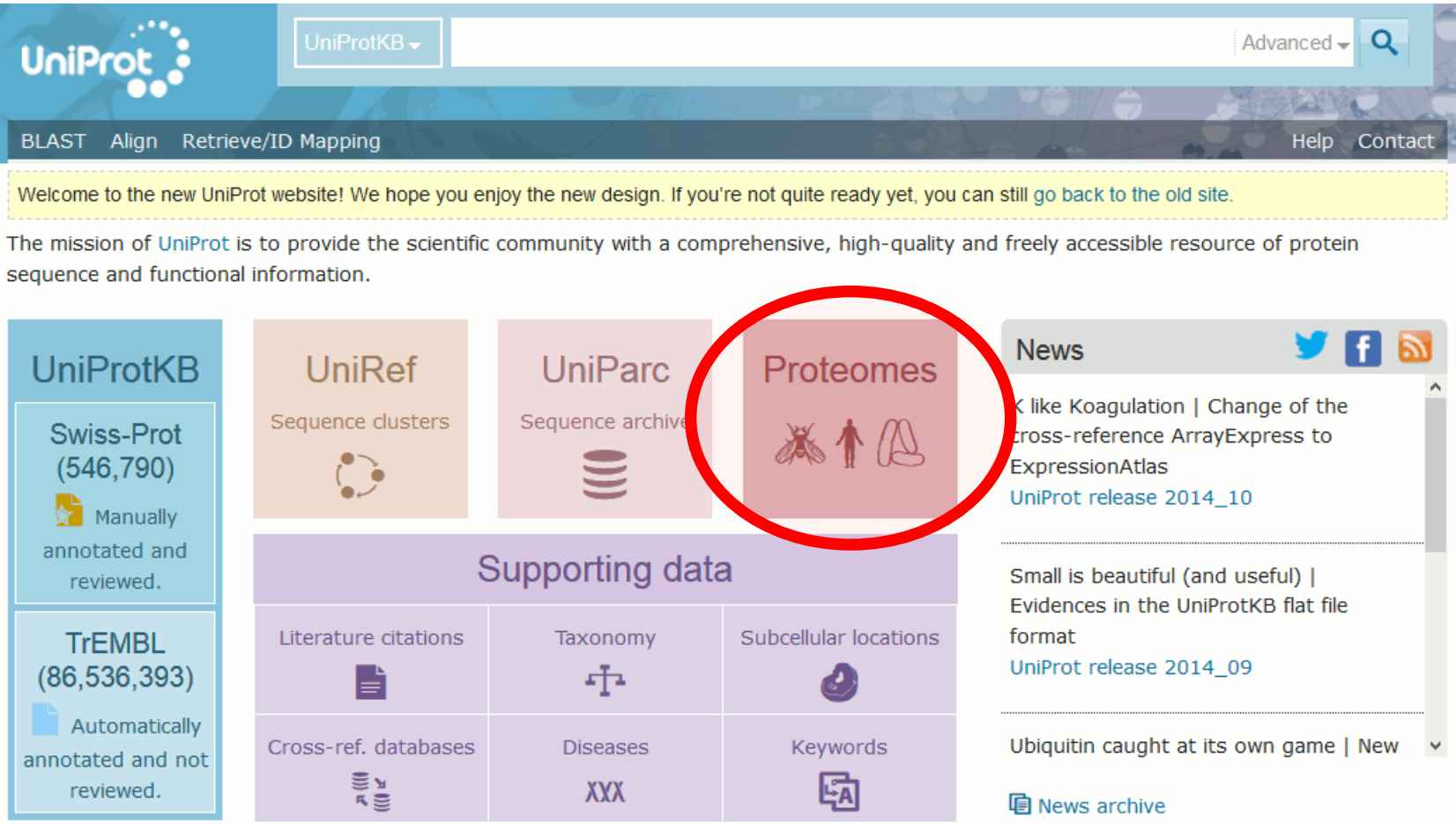
UniSave


UniProt
UniProtKB
Advanced
BLAST
Align
Retrieve/ID Mapping
Help
Contact
Basket
P29466 - CASP1_HUMAN
Protein
Caspase-1
Gene
CASP1
Organism
Homo sapiens (Human)
Status
Reviewed -
- Experimental evidence
Display
None
BLAST
Align
Format
Add to basket
History
Comment (?)
Feedback
Help video
FUNCTION
NAMES & TAXONOMY
SUBCELLULAR LOCATION
PATHOLOGY & BIOTECH
PTM / PROCESSING
EXPRESSION
INTERACTION
Function
Thiol protease that cleaves IL-1 beta between an Asp and an Ala, releasing the mature cytokine which is involved in a variety of inflammatory processes. Important for defense against pathogens. Cleaves and activates sterol regulatory element binding proteins (SREBPs). Can also promote apoptosis.
2 Publications
Catalytic activity
Strict requirement for an Asp residue at position P1 and has a preferred cleavage sequence of Tyr-Val-Ala-Asp-|-.
Enzyme regulation
Specifically inhibited by the cowpox virus Crma protein.
Sites

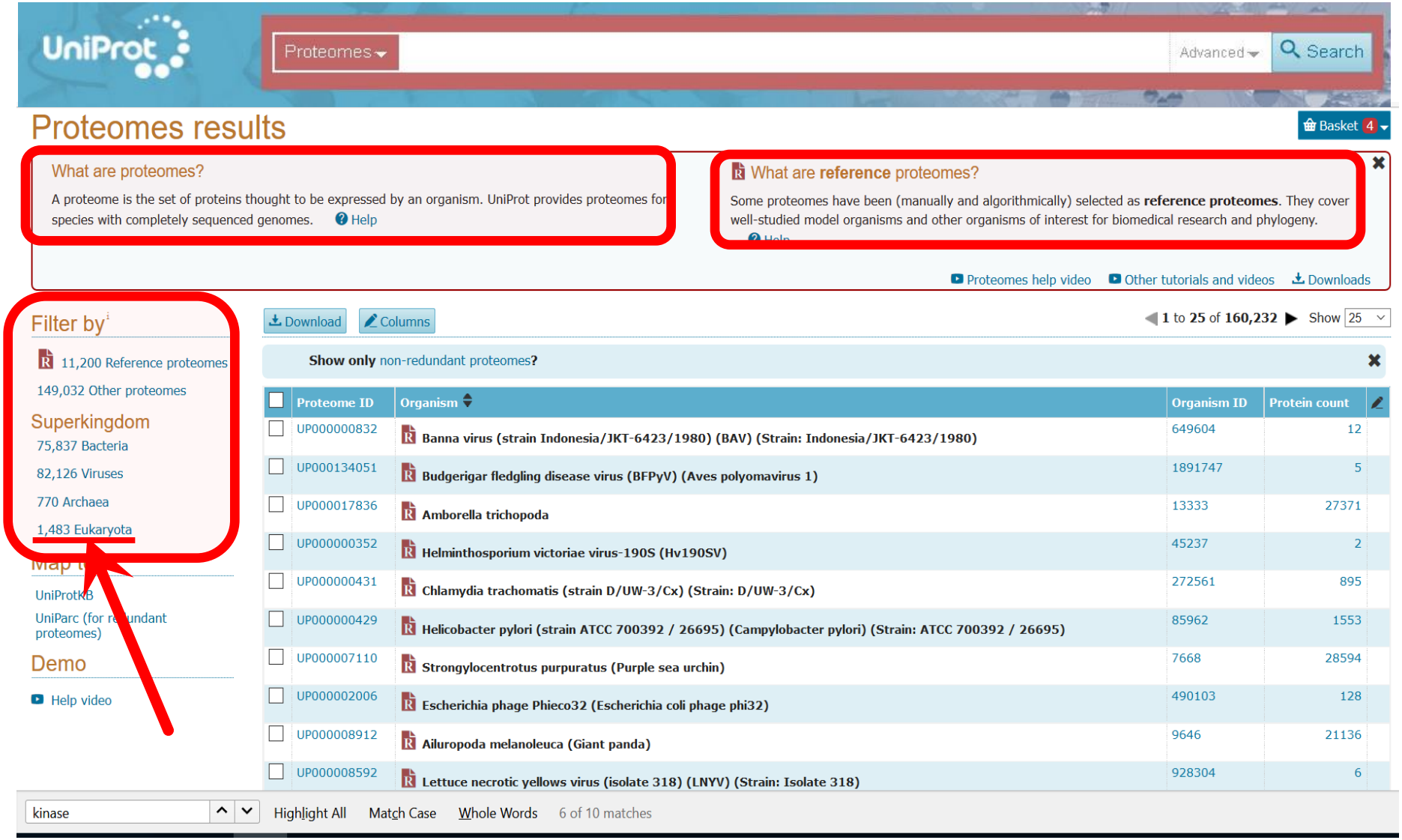
UniProt – BLAST, Align, ID Mapping



Proteomes Section

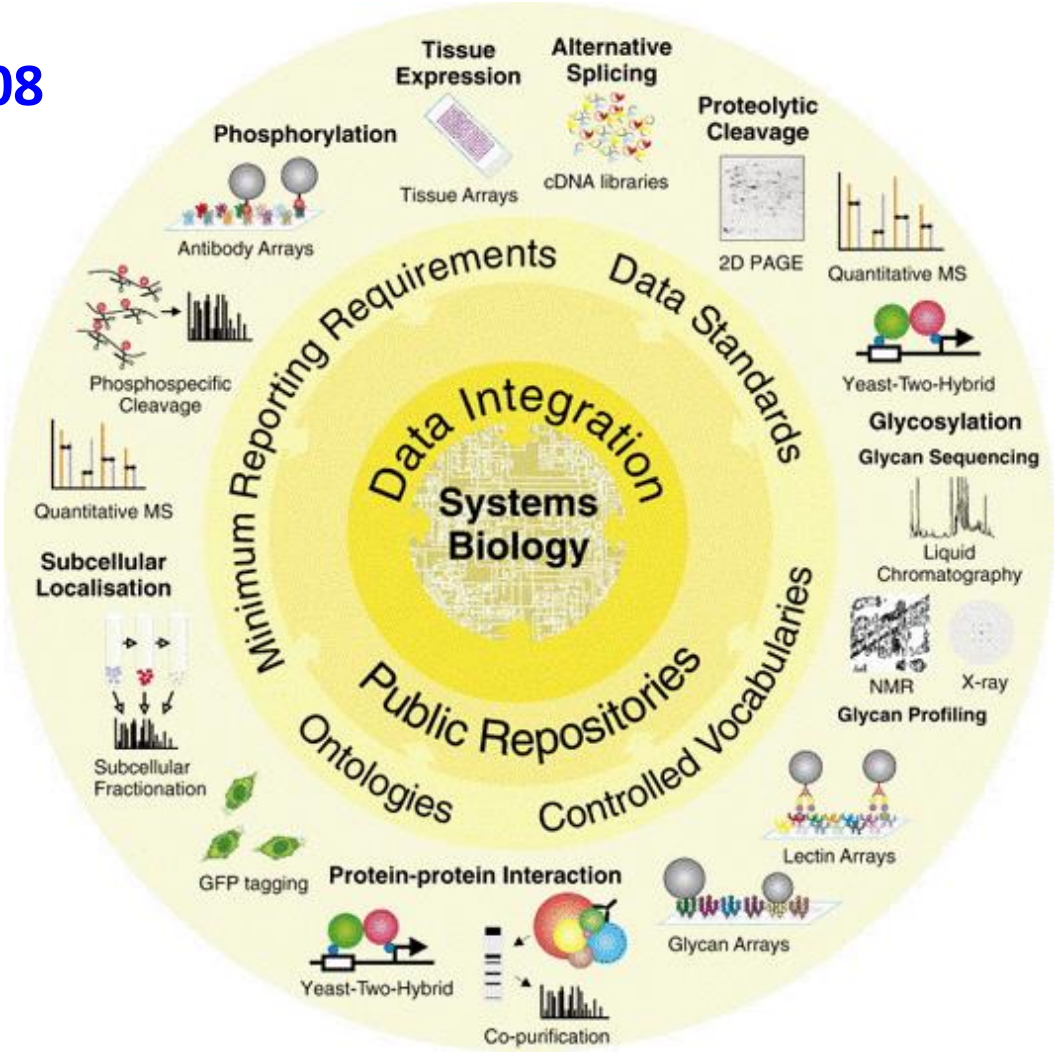


Proteomes Section



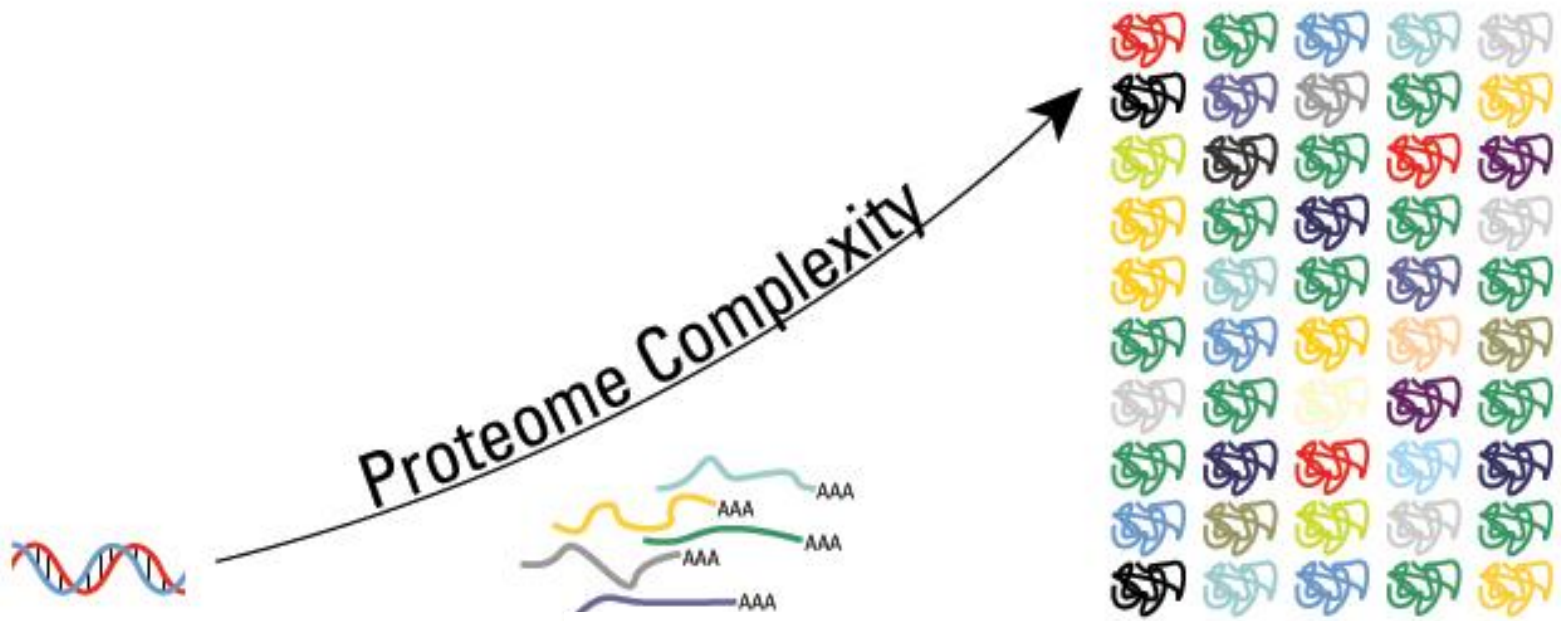
Annotating the human proteome

September 2008
First draft of the complete human proteome available in UniProtKB/ Swiss-Prot.



Gene prediction algorithms, plus the existing transcript and protein information, have enabled the identification of most exons in a genome.

The Human Proteome



Genome
≈20-25,000 genes

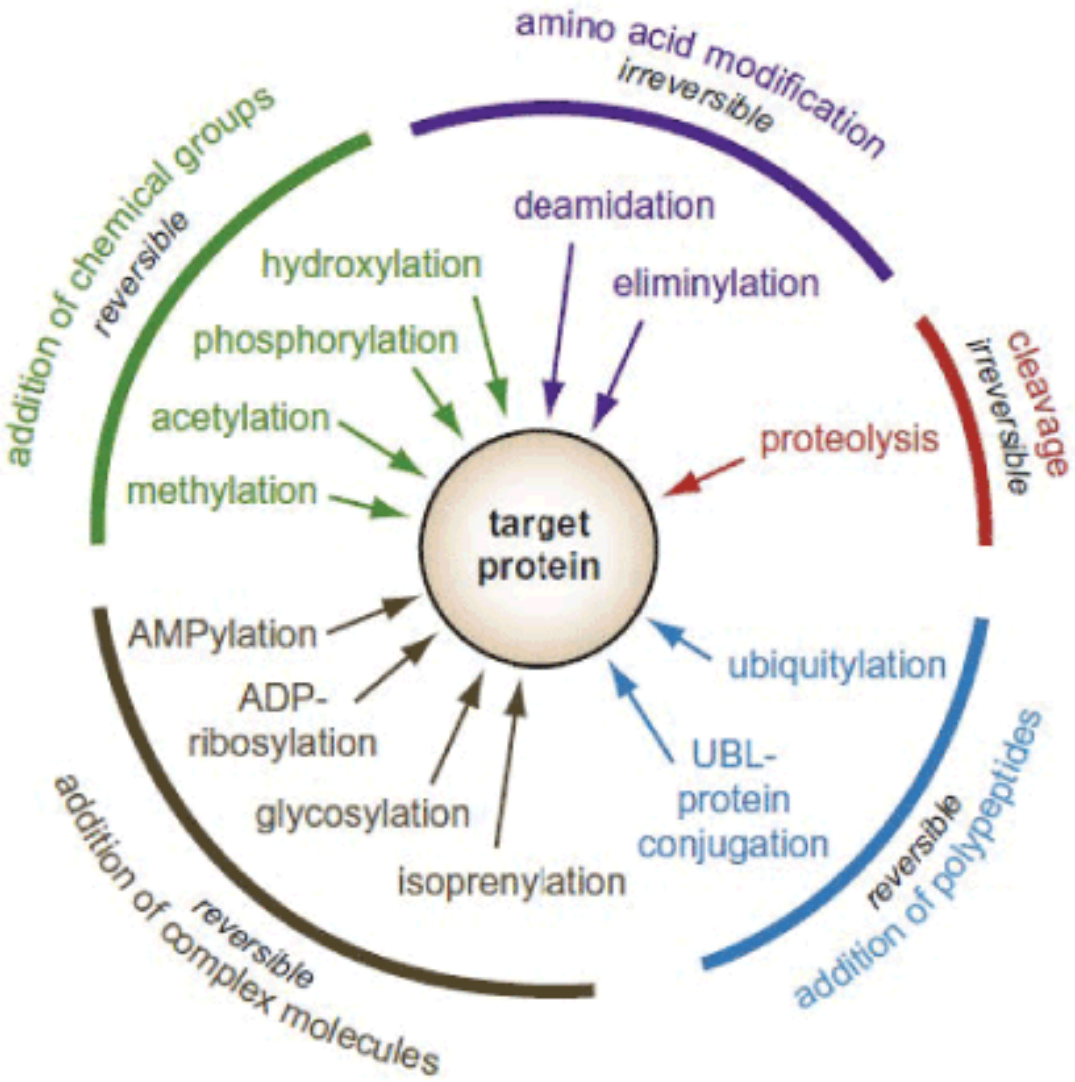
Alternative promoters
Alternative splicing
mRNA editing

Transcriptome
≈100,000 transcripts

Post-translational
modifications

Proteome
>1,000,000 proteins

Post Translational Modifications (PTMs)



Comparison of *in vivo* and *in vitro* environment

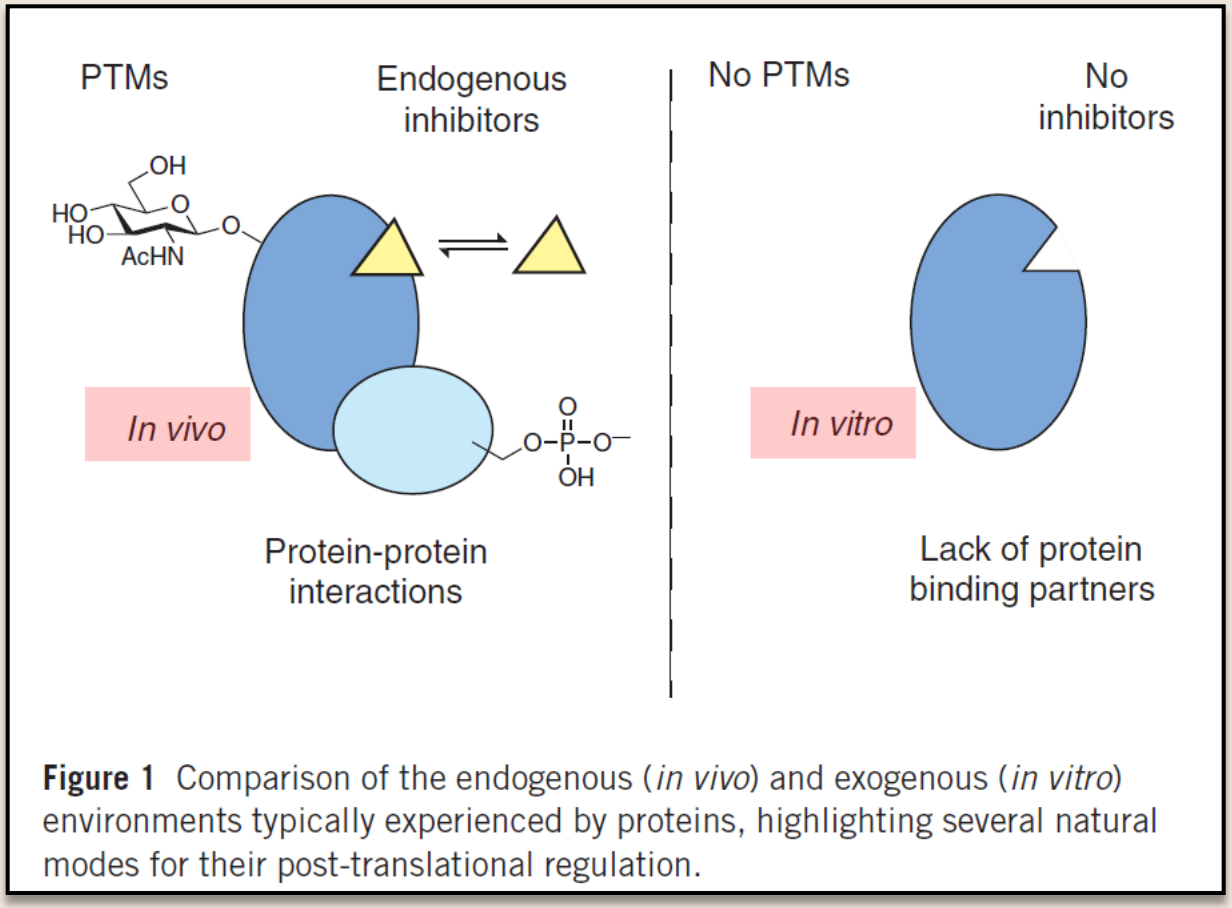


Figure 1 Comparison of the endogenous (*in vivo*) and exogenous (*in vitro*) environments typically experienced by proteins, highlighting several natural modes for their post-translational regulation.

A. Saghatelian & B.F. Cravatt **Assignment of protein function in the postgenomic era** (2005) *Nature Chemical Biology* 1, 130.

UniProt (7) – PTMs

A. Which percentage of the whole SwissProt database has PTMs?

B. Go to the entry with Accession Number: P00533. Find out which PTMs are reported, and which are the evidence for them. Watch them also in the «feature viewer» mode.

Uniprot access from programs

Technical corner

Last modified March 13, 2015

UniProtKB entry view manual
User manual for the UniProtKB entry view.

UniProtKB flat file manual
User manual for the UniProtKB flat file format.

FASTA headers
Description of FASTA headers for UniProtKB (including alternative isoforms), UniRef, UniParc and archived UniProtKB versions.

UniProtKB query fields
List of supported fields for querying UniProtKB on this web site.

Browser support
Recommended list of major web browsers for the UniProt website.

How can I access resources on this web site programmatically?
FAQ with examples of web access using simple URLs (REST).

Parsing SwissProt with BioPhython

http://biopython.org/DIST/docs/api/Bio.SwissProt-pysrc.html

```
#python code
import Bio.SwissProt as sp
example_filename = "./P01892.txt"
with open(example_filename) as handle:
    records = sp.parse(handle)
    for record in records:
        print(record.entry_name)
        print(",".join(record.accessions))
        print(record.keywords)
        print(repr(record.organism))
        print(record.sequence[:20] + "...")
```

```
1A02_HUMAN
P01892,O19619,P06338,P10313,P30444,P30445,P30446,P30514,Q29680,Q29837,Q29899,
Q95352,Q95380,Q9TPX8,Q9TPX9,Q9TPY0,Q9TQH5,Q9TQI3
['3D-structure', 'Complete proteome', 'Direct protein sequencing', 'Disulfide bond',
'Glycoprotein', 'Host-virus interaction', 'Immunity', 'Membrane', 'MHC I', 'Phosphoprotein',
'Polymorphism', 'Reference proteome', 'Signal', 'Transmembrane', 'Transmembrane helix',
'Ubl conjugation']
'Homo sapiens (Human).'
MAVMAPRTLVLLLSGALALT...
```

Uniprot access from programs

https://www.ebi.ac.uk/training/online/course/accessing-em 80% Search

Training | Train online | About Train online | Glossary | Support and feedback | Login/register

EMBL-EBI, programmatically: take a REST from manual searches

- Introduction to EMBL-EBI resources
- Introduction to programmatic access
- Europe PMC, programmatically
- Ensembl, programmatically
- **UniProt, programmatically**
- PDBe, programmatically
- ChEMBL, programmatically
- Sequence analysis tools, programmatically
- EVA, programmatically
- Summary
- Your feedback
- Contributors

UniProt, programmatically

UniProt aims to provide the scientific community with the highest quality, most comprehensive and most thoroughly annotated protein resource. Our mission includes curating detailed information on protein function and sequences including isoforms and disease variants. The UniProt knowledgebase contains millions of sequences, a subset of which have been curated by experts who critically review experimental and predicted data for each protein. The remainder are automatically annotated based on rule systems that rely on the expert curated knowledge. You can learn more about UniProt in UniProt: Exploring protein sequence and functional information or our introductory webinar.

This webinar took place on 20th June 2017 and will introduce the UniProt REST API. In this webinar we will:

- Introduce the UniProt resources (1:12)
- Search the UniProt Knowledgebase (3:40)
- Convert between different database identifiers (11:43)
- Search with proteomics peptides (16:55)
- Show you where to get help (21:47)

UniProt (8) – Searches

⇒ **Questionnaire on UniProt #3**

Errors in Databases ?

Issue: Automatic Enzymes Functional Annotations in Biological Databases

For over a decade, the majority of sequences found in public databases have been annotated using computational prediction alone, following the principle that proteins with similar sequences and similar structures frequently carry out similar functions.

But protein sequence or structure similarity alone does not necessarily equate to cellular or molecular functional similarity.

doi: 10.1016/S0022-2836(02)00016-5 available online at http://www.idealibrary.com on IDEAL® J. Mol. Biol. (2002) 318, 595–608

JMB

Enzyme Function Less Conserved than Anticipated

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The level of sequence similarity that implies similarity in protein structure is well established. Recently, many groups proposed thresholds for similarity in sequence implying similarity in enzymatic function. All previous results suggest the strong conservation of enzymatic function above levels of 50% pairwise sequence identity. Here, I argue that all groups substantially overestimated the conservation of enzyme function because their data sets were either too biased, or too small. An unbiased analysis suggested that less than 30% of the pair fragments above 50% sequence identity have entirely identical EC numbers. Another surprising finding was that even BLAST *E*-values below 10^{-50} did not suffice to automatically transfer enzyme function without errors. As expected, most mis-

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

Annotation Error in Public Databases: Misannotation of Molecular Function in Enzyme Superfamilies

2009

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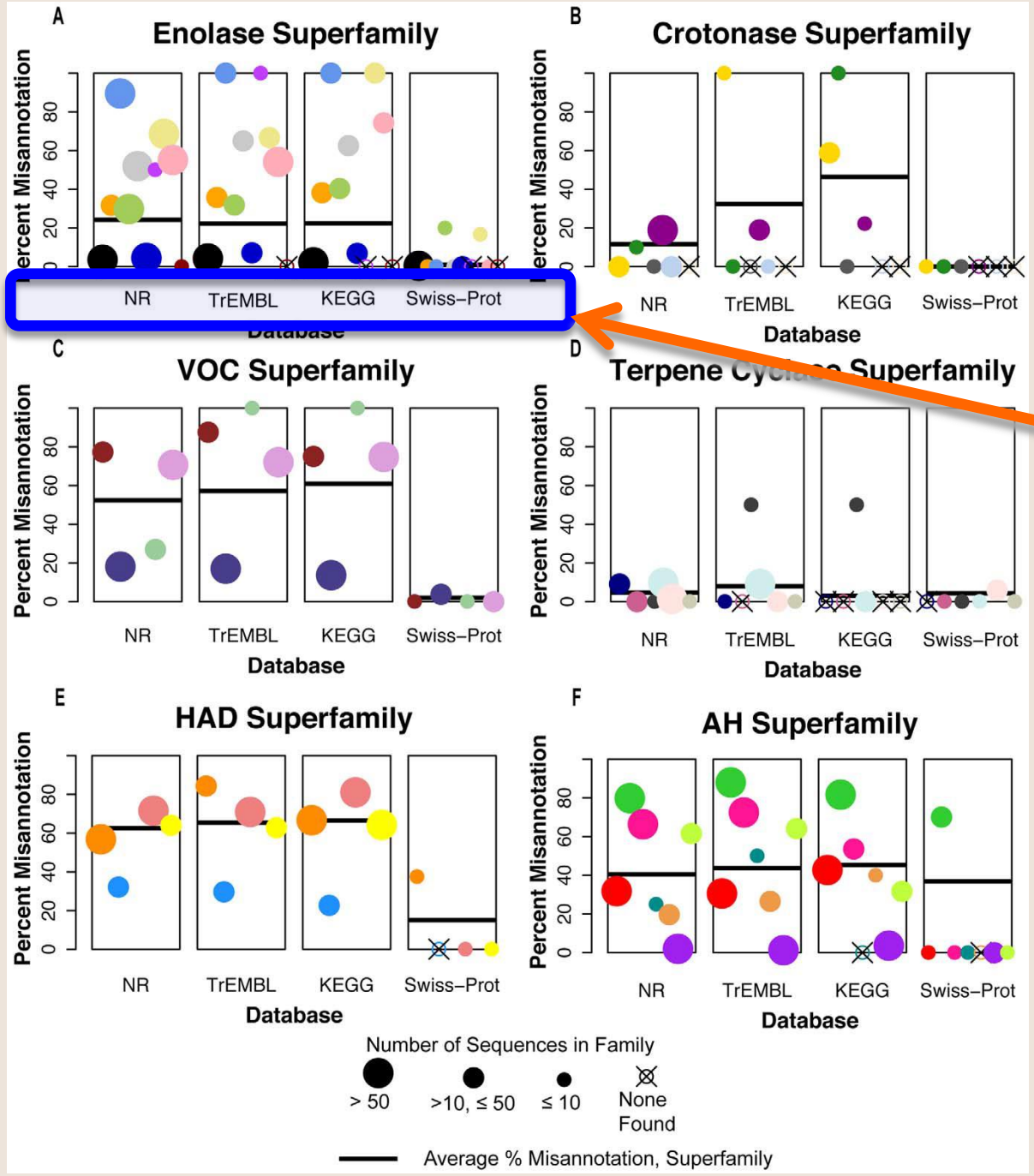
Abstract

Due to the rapid release of new data from genome sequencing projects, the majority of protein sequences in public databases have not been experimentally characterized; rather, sequences are annotated using computational analysis. The level of misannotation and the types of misannotation in large public databases are currently unknown and have not been analyzed in depth. We have investigated the misannotation levels for molecular function in four public protein sequence databases (UniProtKB/Swiss-Prot, GenBank NR, UniProtKB/TrEMBL, and KEGG) for a model set of 37 enzyme families for which extensive experimental information is available. The manually curated database Swiss-Prot shows the lowest annotation error levels (close to 0% for most families); the two other protein sequence databases (GenBank NR and TrEMBL) and the protein sequences in the KEGG pathways database exhibit similar and surprisingly high levels of misannotation that average 5%–63% across the six superfamilies studied. For 10 of the 37 families examined the level of misannotation in one or more of these databases is >80%. Examination of the NR database over time shows that misannotation has increased from 1993 to 2005. The types of misannotation that were found fall into several categories, most associated with "overprediction" of molecular function. These results suggest that misannotation in enzyme superfamilies containing multiple families that catalyze different reactions is a larger problem than has been recognized. Strategies are suggested for addressing some of the systematic problems contributing to these high levels of misannotation.



Percent misannotation in the tested families and superfamilies

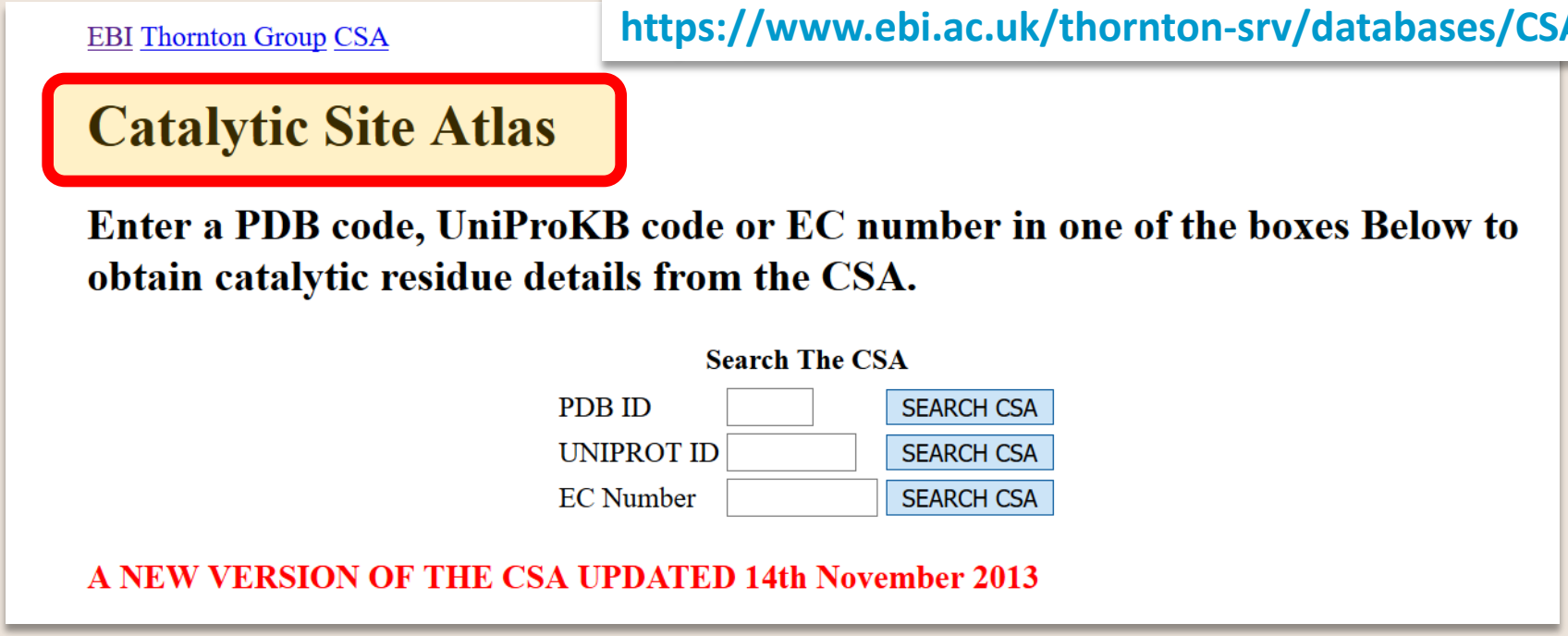
Databases tested:

- **GenBank NR**
  (Non-Redundant)
- **UniProtKB-TrEMBL**
- **KEGG**
  (Kyoto Encyclopedia of Genes and Genomes)
- **UniProtKB-SwissProt**

Schnoes AM, Brown SD, Dodevski I, Babbitt PC. **Annotation error in public databases: misannotation of molecular function in enzyme superfamilies,** PLoS Comput Biol. 2009

What about using conservation of known catalytic residues to improve the annotation of catalytic function?

https://www.ebi.ac.uk/thornton-srv/databases/CSA/



Using the conservation of known catalytic residues has been shown to greatly improve coverage and accuracy in transferring annotations to low-sequence-similarity homologs, at sequence identity thresholds below 40%, though problems still exist.