Public Databases in Health and Life Sciences

“the potential to translate big data into big discovery”

Academic year 2023-2024

Public Databases in Health and Life Sciences

Lesson 1. Organizing biological knowledge in databases.

- Technical concepts and definitions.
- Different classifications of biological databases.
- Hierarchical organization of life and levels of annotation.

Practical session #1

- Introduction to the NCBI and the *Entrez* system
- Tools for online databases search and retrieval (part I).

What is a database?

Dictionary definition

Database : A usually large collection of data organized specially for rapid search and retrieval. (as by a computer)

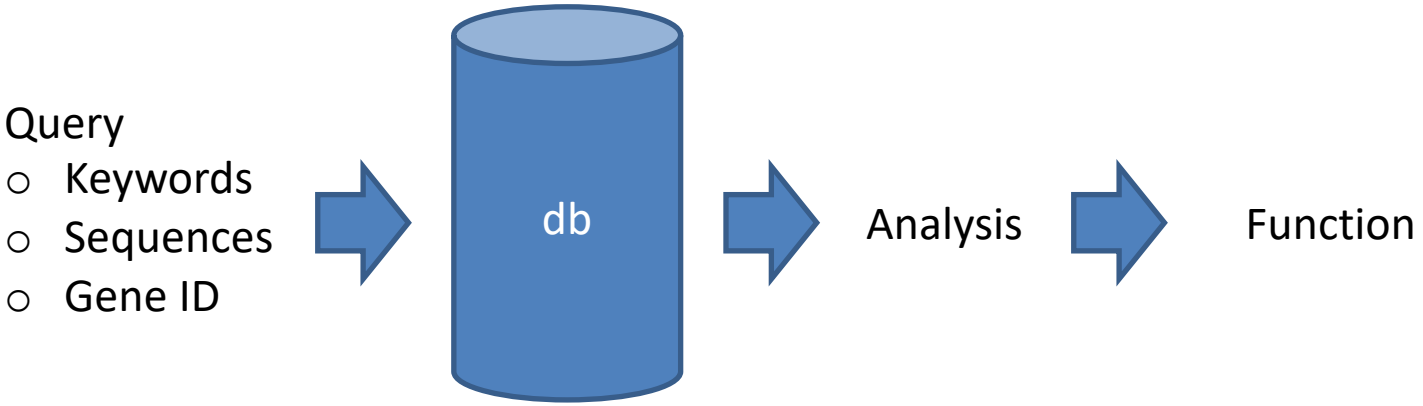
The Oxford English dictionary cites a 1962 technical report as the first to use the term "data-base.“

What is a database?

A collection of related data, which are:

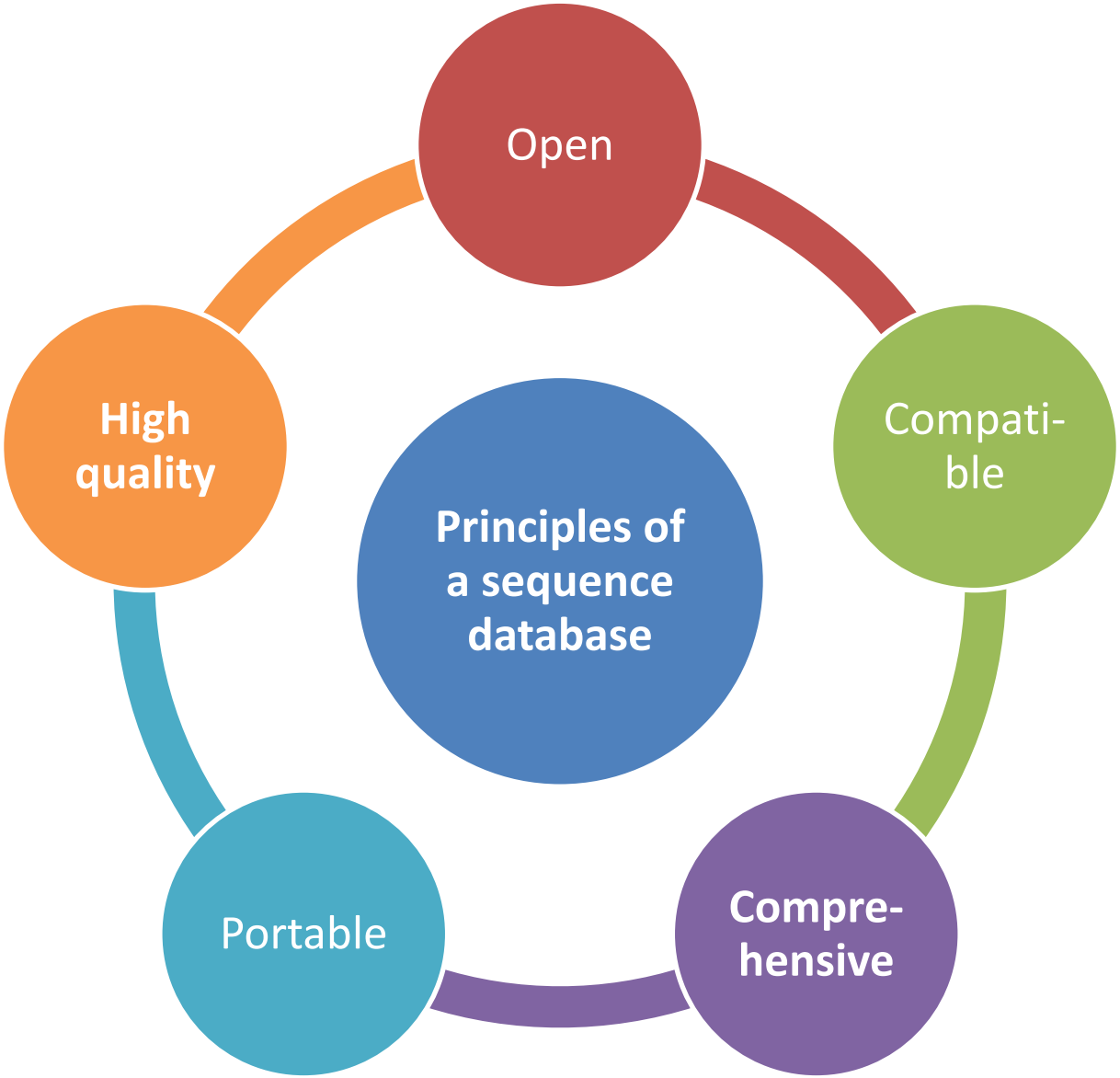
- Structured
- Searchable (index)
- Updated periodically (releases)
- Cross-referenced (hyperlinks)

You will need an appropriate database management system (DBMS)!



How Databases should be?

Taken from http://www.ebi.ac.uk/services



What is a database?

- A collection of related data elements
  - *Tables*
    - *columns (fields)*
    - *rows (records)*
  - *Documents*
    - *Key -> Value*
- Records retrieved using a query language
- Database technology is well established

Relational Databases

Rows (records)

- actual data
- whereas *fields* describe what data is stored, the *rows* of a table are where the actual data is stored

Columns (fields)

- attributes of tables, e.g. for *citation* table, *title, journal, volume, author*

How is information organized in databases?

Accession numbers and Identifiers

An **Identifier** is essentially a name of a database, table, or table column.

- As the creator of the database, you are free to identify these objects as you please.
- The identifier can change (based on the curator)

Each record (row in the table) has a **unique identifier**, alone or combined with another column is unique for that table. **The primary key (accession number or accession code)**.

- The primary key should not change.
- Data is indexed according this primary key
- The unique identifier serves to identify the data stored in this record across all the tables in the database (relational database).
- Usually, a string of letters and digits that uniquely identifies an entry in its database.
  - The accession number for TPIS_CHICK in Uniprot/Swissprot is P00940

How is information organized in databases?

Accession numbers and Identifiers

Some DBs have both Identifiers and accession as unique for each entry in the DB.

In these cases, the main difference is that Identifiers are Human readable and accession are just "random" codes.

Example Pfam_ID: MlaC; Pfam_AC: PF05494

In some cases Identifiers are mutable (but remain unique) while accessions are not

in UniprotKB accession P0AAP1 Use to have ADRA_ECOLI as Id (Name) but no it is DGCC_ECOLI

The fact that they are called "unmutable" does not mean that can not be considered obsolete and removed from the database.

Sometimes accessions can have a version number, which means that something has changed, but whatever they represent remains
Examples:
In Pfam the current accession with version for the MlaC family is PF05494.15
In ncbi refseq nuccleotide, the current accession for *Neisseria meningitidis MC58* complete genome is NC_003112.2

Biological Databases

- Thousands biological databases
    - Many of the major ones covered in the annual Database Issue of Nucleic Acids Research (NAR) (2018: 1737 listings 2022:1645). It is available at http://www.oxfordjournals.org/nar/database/c/
- Vary in size, structure, quality, coverage, level of interest, data origin …
- Generally accessible through the web

Limitation and challenges of biological databases

- Each of the database resources contains a different subset of biological knowledge.

- There is not standard format
    - Every database or program has its own format for storing or presenting data (eg: http://current.geneontology.org/ontology/go-basic.obo)

- There is not standard nomenclature
    - Every database has its own names (Controlled vocabularies)

- Data is not fully optimized
    - Some datasets have missing information without indication of it

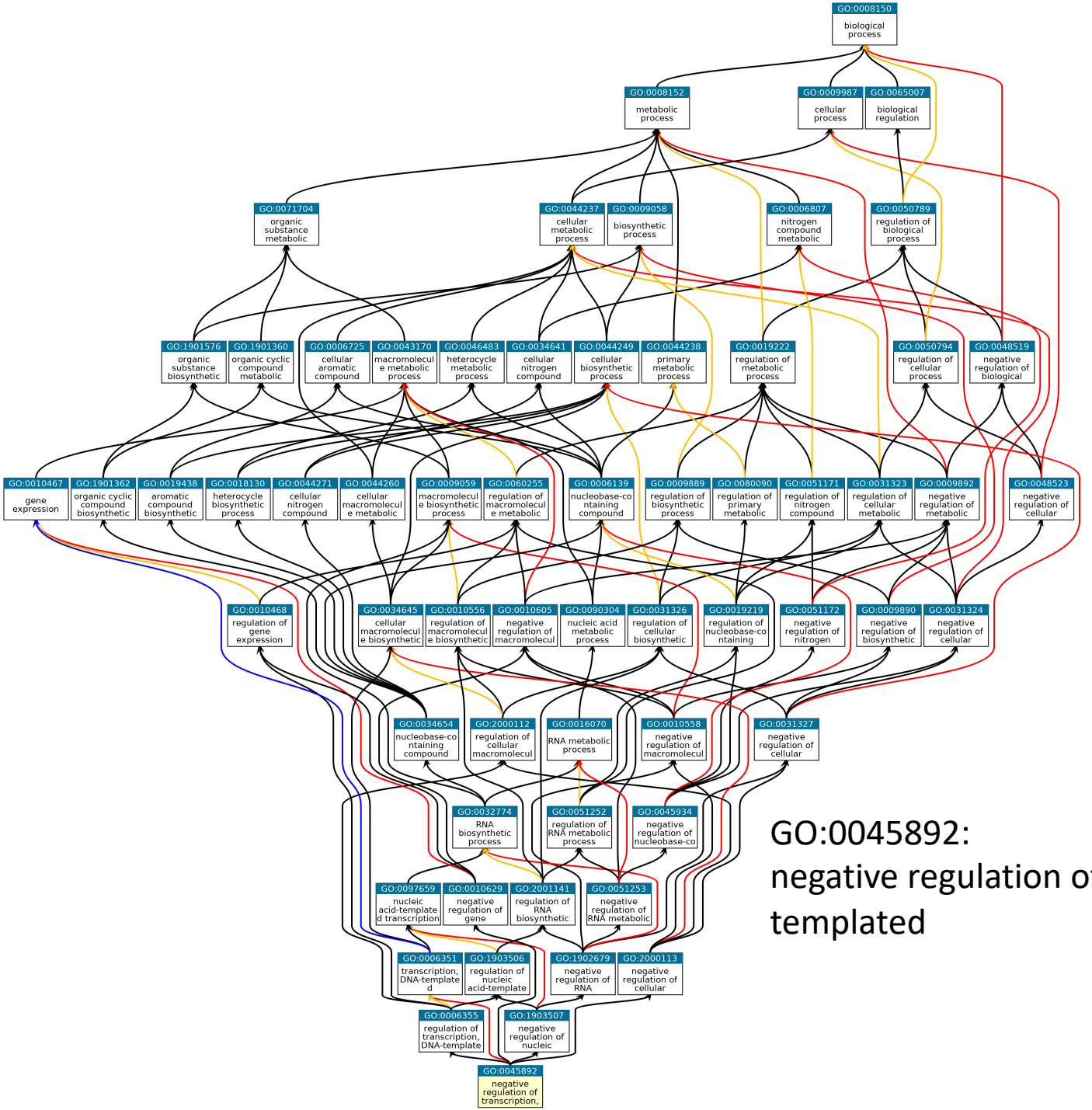
- Data errors
    - Data is some time of poor quality, erroneous, misspelled
    - Error propagation resulting from computer annotation

- The integration of biological data remained an additional challenge
    - Different DBMS
    - Name of biological objects across databases (Controlled vocabularies)
    - Biological databases are continuously changing
    - Clash of concepts

Controlled vocabularies are a vital ingredient for annotating data stored in databases.

- Non-hierarchical controlled vocabularies
  - the simplest type of controlled vocabularies are non-hierarchical lists of terms
- Thesaurus as a controlled and structured vocabulary in which concepts are represented by terms
- Taxonomy as a classification scheme
  - you can find everything annotated as a sub-category of the search term
- Using ontologies
  - an ontology describes the categories of objects described in a body of data, the relationships between those objects, and the relationships between those categories (Directed Acyclic Graph)
  - *E.g*. the Gene Ontology (GO) describes the function and cellular localization of gene products across all species. Eg GO:0045892

EMBL-EBI Train online
Bioinformatics for the terrified
https://www.ebi.ac.uk/training/online/courses/bioinformatics-terrified/



GO:0045892:
negative regulation of transcription, DNA-templated

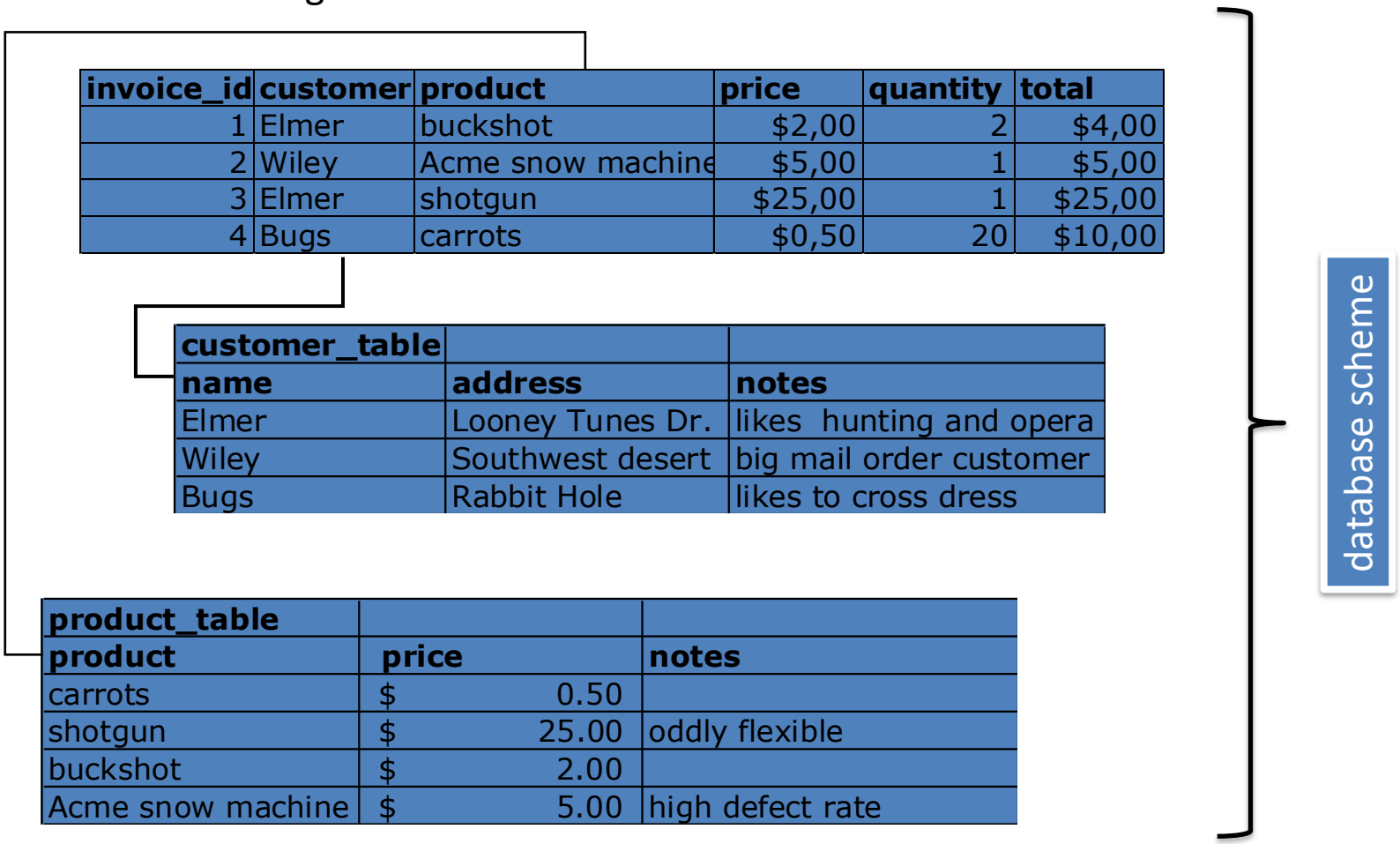
What is a flat file database?

- Sequential collection of entries, stored in a set of text files
- Flat-File databases can be represented as holding all of their data in one table only (two-dimensional table)
- Files written in plain text, standard defined format. Examples:
  - Each line is a record. Fields are separated by delimiters: tabs, commas…
  - Each file is a record. Fields expressed as key->value (eg: json db)
- Searching issues!

Accesion	Source	Gene	Mol Type
AF068625.2	Mus musculus	dnmt3a	mRNA
HD654844.1	Homo sapiens	hba1	mRNA
AD836734.3	Escherichia coli	recA	DNA
BD823723.5	Homo sapiens	hpo3	DNA
TF7823562.1	VIH	p17	cDNA
AS9832656.3	Homo sapiens	hbb	DNA
AF6723523.1	Danio rerio	egf2	mRNA

What is a relational database?

- A relational database contains multiple tables and defines the relationships between them.
- Virtually all use SQL (Structured Query Language) as a language for querying and maintaining



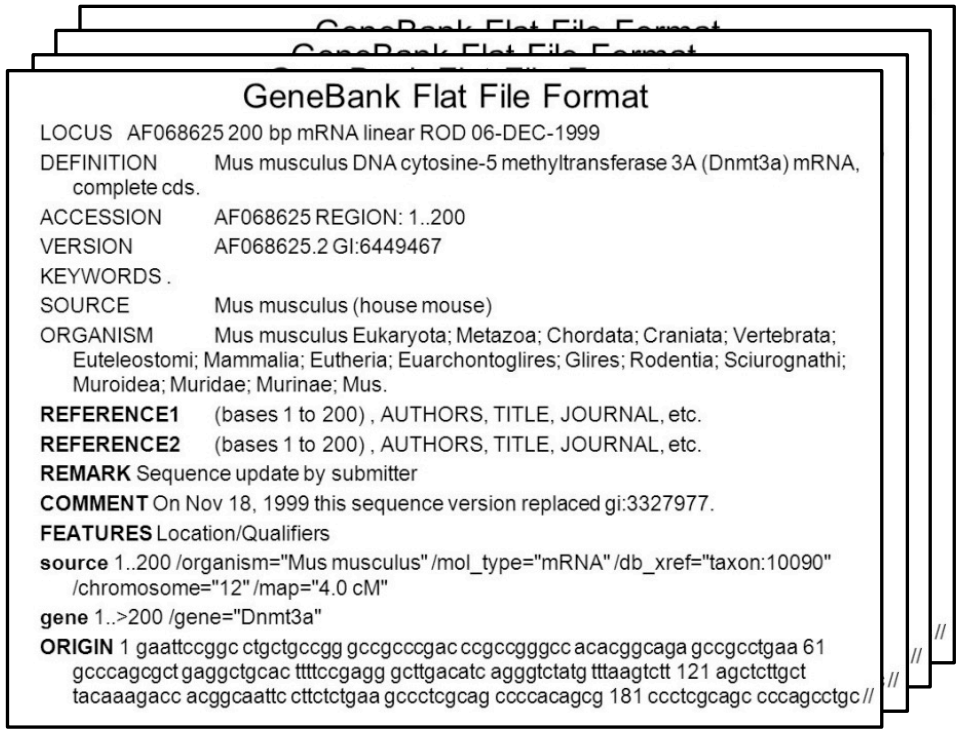
invoice_id	customer	product	price	quantity	total
1	Elmer	buckshot	$2,00	2	$4,00
2	Wiley	Acme snow machine	$5,00	1	$5,00
3	Elmer	shotgun	$25,00	1	$25,00
4	Bugs	carrots	$0,50	20	$10,00

customer_table		
name	address	notes
Elmer	Looney Tunes Dr.	likes hunting and opera
Wiley	Southwest desert	big mail order customer
Bugs	Rabbit Hole	likes to cross dress

product_table		
product	price	notes
carrots	$ 0.50	
shotgun	$ 25.00	oddly flexible
buckshot	$ 2.00	
Acme snow machine	$ 5.00	high defect rate

database scheme

A common way of storing biological data in a structured manner is to use a relational database



GeneBank Flat File Format

LOCUS AF068625 200 bp mRNA linear ROD 06-DEC-1999
DEFINITION Mus musculus DNA cytosine-5 methyltransferase 3A (Dnmt3a) mRNA, complete cds.
ACCESSION AF068625 REGION: 1..200
VERSION AF068625.2 GI:6449467
KEYWORDS .
SOURCE Mus musculus (house mouse)
ORGANISM Mus musculus Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Sciurognathi; Muroidea; Muridae; Murinae; Mus.
REFERENCE1 (bases 1 to 200) , AUTHORS, TITLE, JOURNAL, etc.
REFERENCE2 (bases 1 to 200) , AUTHORS, TITLE, JOURNAL, etc.
REMARK Sequence update by submitter
COMMENT On Nov 18, 1999 this sequence version replaced gi:3327977.
FEATURES Location/Qualifiers
source 1..200 /organism="Mus musculus" /mol_type="mRNA" /db_xref="taxon:10090" /chromosome="12" /map="4.0 cM"
gene 1..>200 /gene="Dnmt3a"
ORIGIN 1 gaattccggc ctgctgccgg gccgcccgac ccgccgggcc acacggcaga gccgcctgaa 61 gcccagcgct gaggctgcac ttttccgagg gcttgacatc agggtctatg tttaagtctt 121 agctcttgct tacaaagacc acggcaattc cttctctgaa gccctcgcag ccccacagcg 181 ccctcgcagc cccagcctgc //

tab1

Accesion	Source	Gene	Mol Type
AF068625.2	Mus musculus	dnmt3a	mRNA
HD654844.1	Homo sapiens	hba1	mRNA
AD836734.3	Escherichia coli	recA	DNA
BD823723.5	Homo sapiens	hpo3	DNA
TF7823562.1	VIH	p17	cDNA
AS9832656.3	Homo sapiens	hbb	DNA
AF6723523.1	Danio rerio	eqf2	mRNA

tab2

Species	TaxID	Synonym
Homo sapiens	9606	Human
Mus musculus	10090	Mouse
Danio rerio	7955	Zebra fish
Escherichica coli	562	E. coli

Essential aspects of primary and secondary databases.

	Primary database	Secondary database
Synonyms	Archival database	Curated database; knowledgebase
Source of data	Direct submission of experimentally-derived data from researchers (database staff organize but don't add additional information)	Results of analysis, literature research and interpretation, often of data in primary databases
	Once given a database accession number, the data in primary databases are never changed: they form part of the scientific record.	Continuously updated Biocuration

EMBL-EBI Train online
Bioinformatics for the terrified
https://www.ebi.ac.uk/training/online/courses/bioinformatics-terrified/what-makes-a-good-bioinformatics-database/primary-and-secondary-databases/

Definition and aims of biocuration

Biocuration involves the interpretation and integration of information relevant to biology into a database or resource that enables integration of the scientific literature as well as large data sets.

Primary goals of biocuration.

- Accurate and comprehensive representation of biological knowledge
- Easy access to this data for working scientists and a basis for computational analysis

How to access the data ?

Databases Search and Retrieval

A request of data from a Database is called as *Query*

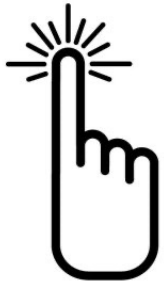
Queries can be of three forms:

1. Choose from a list of parameters
2. Query by example (QBE)
    - QBE build wizard allows which data to display
3. Query language
    - SQL (structured query language)

How to access the data in public databases ?

Human Web interface (web based, small scale)

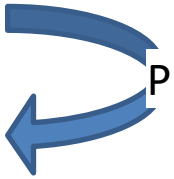
- Free text search
- Common mode of search are keywords with modifiers or identifiers
- Cross-references link the information of different databases
- You do not see the underlying database structure
- Output defined by host/provider



"click your way"

Web services and Programmatic data access

- Application Programmers Interface (API)
- To approach database programmatically



Programming Utilities Web Service

Download the data: File Transfer Protocol (FTP), rsync, http

- Flat files (script based, bulk data download)

Database searching tips to choose from a list of parameters

- Using keywords and enclose phrases in double quotes
- Boolean searches

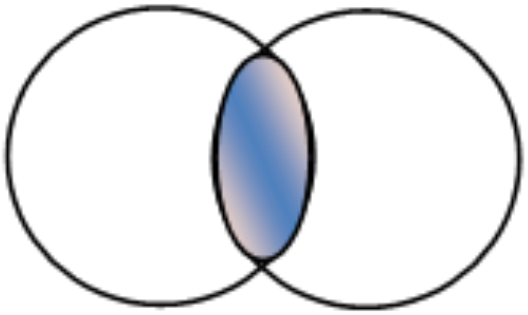
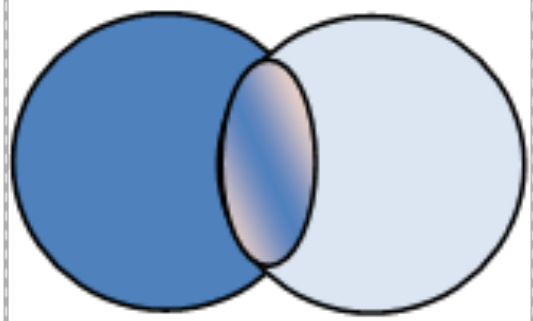
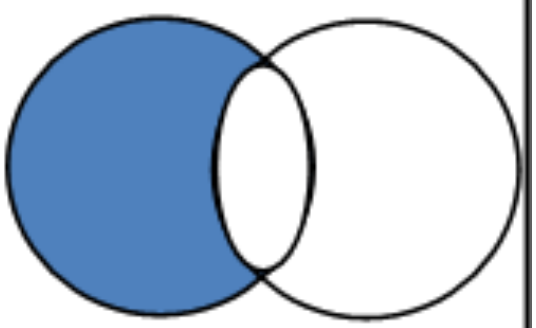
  Boolean logic consists of three logical operators:

  OR

  AND

  NOT
- Wildcards or Query Truncation
- Advance searches by using search tags and fielded searching

Searching Strategies: Boolean operators

cats **AND** dogs	cats **OR** dogs	cats **NOT** dogs
		
retrieves items that contain both terms	retrieves items that contain either term	retrieves items that contain only one term
Restrict	**Expand**	**Filter**

Searching with wildcards or query truncation.

- Truncation: Wildcards are useful if, for example, you wish to search for a group of words (e.g., all words starting with “cell” and ending with “ase”) or if it is unclear how a word is spelt in a databank.
  - Cell* (NCBI and EMBL)
  - *ase (EMBL)
  - *moglobin (EMBL)

- “?” Matches one character of any value. (EMBL)
  - nif? This expression finds the gene names nifa, nifb, nifc, nifd, nife. But do not words like Nifedipine

Note: Placing a wildcard at the start of a word or string may increase the response time because all words in the index have to be checked against your string.
For example cat* in PubMed, will give incomplete results!

Fielded searching using any of the indexed fields (advanced searches)

Entering the phrase with a [field descriptions]:

robotic surgery [title]
Miller MJ [author]
“protein domain” [TI]
human [Organism]
insulin [Protein Name]

Combining fielded searching with booleans

enzymes [TI] NOT Gonzales P [AU]
human [Organism] AND insulin [Protein Name]

Search for Field Descriptions are different in each Database

NCBI	**UNIPROT**
NC_0000*[Accession]	accession:p62988
Human[Organism]	organism:human
horse[taxonomy]	taxonomy:40674
neoplasms[MeSHTerms]	keyword:neoplasms
prolactin[Protein Name]	name:"prion protein“
APOE[gene]	gene:HSPC233
srcdb_refseq[Properties]	database:(type:pfam)
2010/06[Publication Date]	created:[20121001 TO *]
110:500[Sequence Length]	length:[100 TO 500]
gene_symbol[sym]	go:0015629
1.1.1.53[ecno]	ec:3.2.1.23
gbdiv_est[PROP]	reviewed:yes
: : :	: : :
etc	etc

http://www.ncbi.nlm.nih.gov/entrez/query/static/help/Summary_Matrices.html#Search_Fields_and_Qualifiers
https://www.ncbi.nlm.nih.gov/books/NBK49540/
https://www.uniprot.org/help/query-fields

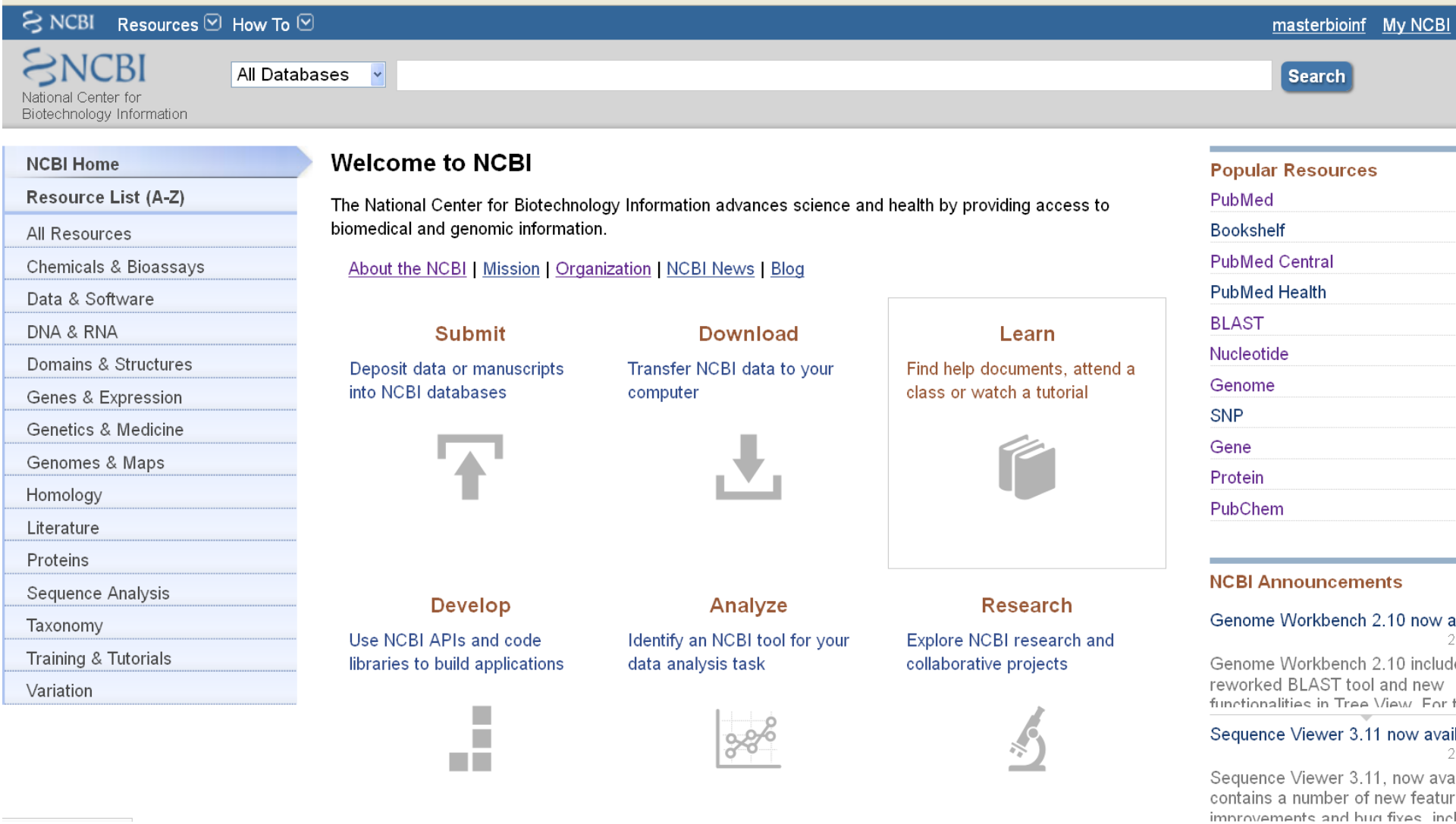
The NCBI is a comprehensive website for biologists (database of databases (of databases))

http://www.ncbi.nlm.nih.gov/gquery/

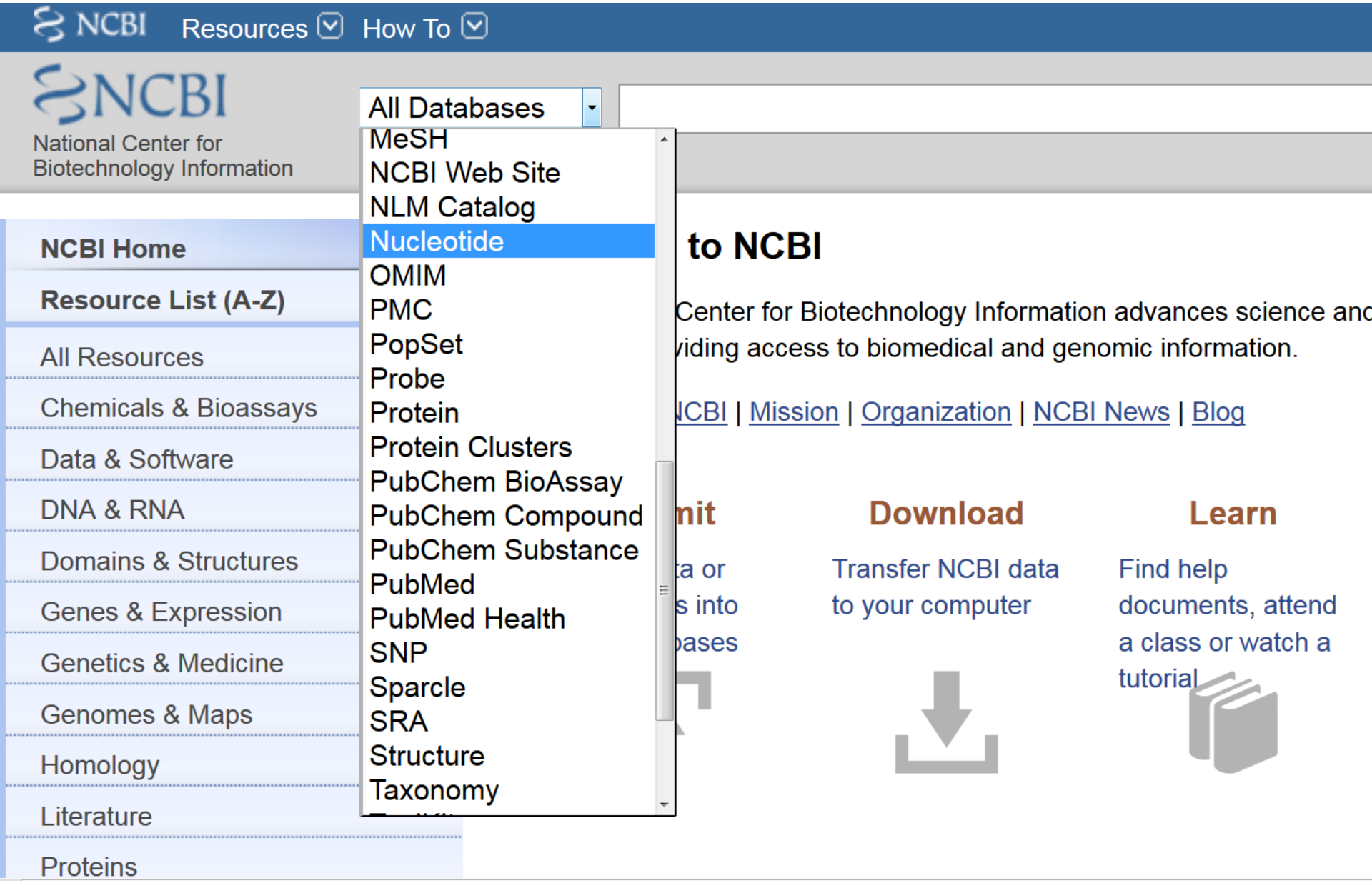
- The National Center for Biotechnology Information (NCBI)
- Created in 1988 as a part of the National Library of Medicine at NIH
- Establish public databases
- Research in computational biology
- Develop software tools for sequence analysis
- Disseminate biomedical information
- Over 30 databases (primary, secondary, specialized, meta-databases, etc.)

The NCBI home page

http://www.ncbi.nlm.nih.gov/



NCBI hosts over 30 databases



How to access the NCBI data ?

***Entrez*: An Integrated Database Search and Retrieval System**

Human Web interface (web based, small scale)

- Free text search
- List of identifiers (Batch *Entrez*)

Web service (Programmatic data access)

- *Entrez* Utilities Web Service (NCBI): The E-utilities
  - Entrez Direct: E-utilities on the Unix Command Line

Searching sequence databases using a sequence query

- BLAST

File Transfer Protocol (FTP)

- Flat files (script based, bulk data download)

Entrez: An Integrated Database Search and Retrieval System

- Access all NCBI resources (Database Integration)

- *Entrez* Databases
  - All Molecular Database entries are organized by organism (Taxonomy Database).
  - Each record is assigned a UID “unique integer identifier” for internal tracking
  - Each record is indexed by data fields: [author], [title], [organism], and many others
  - Each record is given a Document Summary (DocSum).
  - Each record is manually or computationally assigned links to biologically related UIDs in and across databases.

https://www.ncbi.nlm.nih.gov/sites/batchentrez

Batch Entrez

Given a file of Entrez accession numbers or other identifiers, Batch Entrez downloads the corresponding records.

Instructions

1. Start with a local file containing a list of accession numbers or identifiers
2. Select the database corresponding to the type of accession numbers or identifiers in your input file
3. Use the **Browse** or **Choose File...** button to select the input file
4. Press the **Retrieve** button to see a list of document summaries
5. Select a format in which to display the data for viewing, and/or saving
6. Select 'Send to file' to save the file.

Tips

- To download entire genome records, check the NCBI FTP site, instead of using Batch Entrez.
- Some lists of record identifiers can be tens of thousands of lines long, so Batch Entrez may not retrieve all records from one list. Split the list of identifiers into smaller files using a file splitting software or a file split command at the command prompt in UNIX or LINUX systems.
- When loading large numbers of genome records, put several thousand record identifiers per file, one per line, left-adjusted.
- Please note that Batch Entrez will check for duplicate identifiers when reporting results from a list that you have imported.
- When retrieving a list of Nucleotide accessions, you must select the specific component database from which the accessions or GIs were saved. For Nucleotide, choose either the CoreNucleotide, the EST or the GSS selection from the database menu. If you have a mixed list of nucleotide accessions or UIDs, you will need to run the Batch Entrez search three times. Select the database from the pull-down menu, CoreNucleotide, EST, and GSS separately.
- In all cases, be certain to select the database that corresponds to the identifiers you are uploading. For example, if you have saved a list of protein accession numbers, be sure to select the Protein database.

Access Entrez through programs or scripts

Entrez Utilities Web Service (NCBI) The **E-utilities** http://www.ncbi.nlm.nih.gov/books/NBK25500/

• Entrez Programming Utilities are tools that provide access to Entrez data outside of the regular web query interface. You can access them by constructing the right URL and retrieving results. This is the base:
https://eutils.ncbi.nlm.nih.gov/entrez/eutils/
And then you add the desired tool with the appropriate parameters.
Some tools:

- **ESearch: Searches and retrieves primary IDs and retains results in the user's environment.**
- **EFetch: Retrieves records from one or more primary IDs or from the user's environment.**
- Also: **EGQuery, EInfo, ELink, ESpell, Esummary**

Example: Get the PubMed IDs (PMIDs) for articles about breast cancer published in Science in 2008:

https://eutils.ncbi.nlm.nih.gov/entrez/eutils/esearch.fcgi?db=pubmed&term=science[journal] AND breast cancer AND 2008[pdat]&retmode=json

• There is a set of programs implementing these functions. They allow to access the same servicies form the UNIX-like Command Line interface : Entrez Direct. (https://www.ncbi.nlm.nih.gov/books/NBK179288/)

Example: Download all protein sequences in fasta format from *Stenotrophomonas maltophilia* with the word “lactamase” in their title:

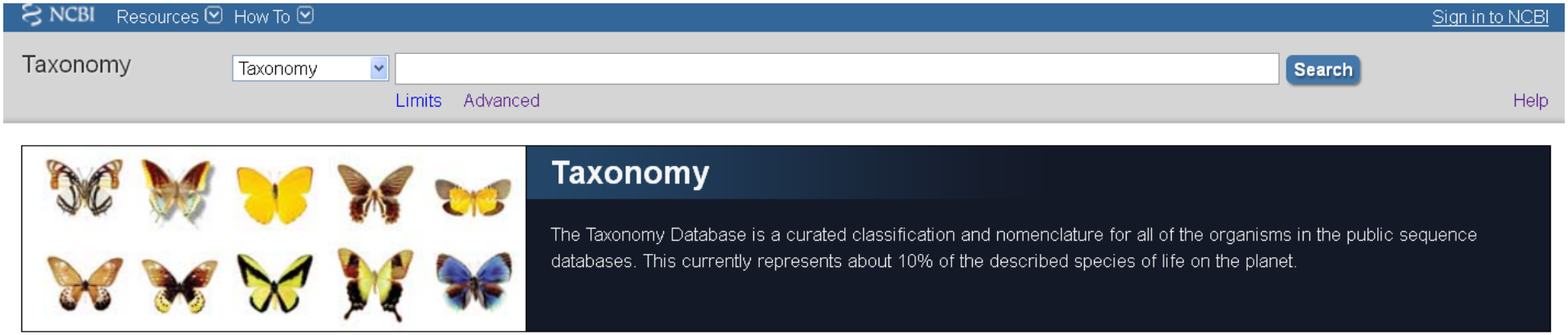
```
~]$ esearch -db protein -query "txid40324[porgn] AND lactamase[TI]"|efetch -format fasta
```

BLAST (Basic Local Alignment Search Tool)

Altschul, *et al*. 1990, *J Mol Biol*, 215:403-10*
Altschul, *et al*. 1997, Nucleic Acids Res, 25(17): 3389–3402
(* one of the most highly cited paper)

- BLAST is an algorithm to find regions of similarity between biological sequences both proteins or nucleic acids
- BLAST compares a query sequence with a library or database of sequences, and identify library sequences that resemble the query sequence above a certain threshold.
- BLAST Home page: http://www.ncbi.nlm.nih.gov/BLAST
- BLAST is one of the most widely used bioinformatics programs

NCBI: Taxonomy DataBase



530 777 (formal) species!

Each taxa with an ID, the **TaxID**

http://www.ncbi.nlm.nih.gov/taxonomy/

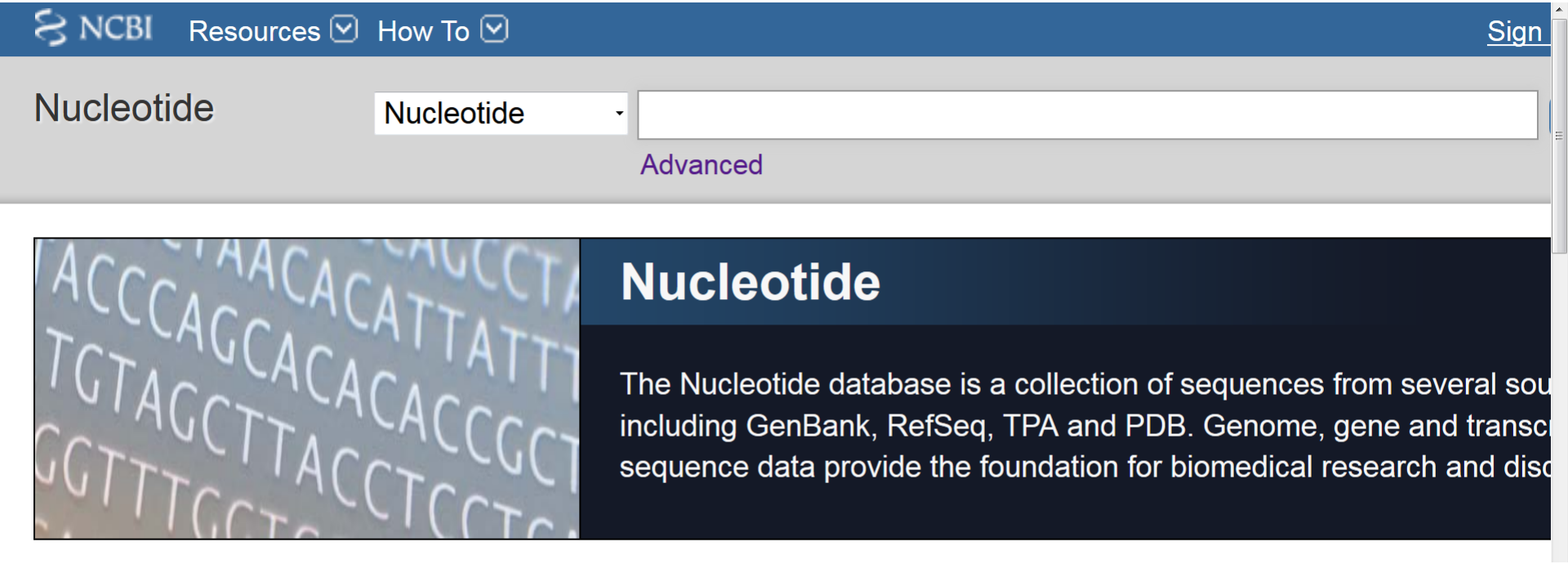
NCBI:Molecular Sequence Databases

Sequence Databases (Primary)

- Nucleotide (GenBank)
  - PopSet
  - SRA, GSS
- Protein

Marker Databases

- Single Nucleotide Polymorphisms (SNP's, dbSNP)
- Sequence Tagged Sites (STS's, dbSTS)
- Expressed Sequence Tags (EST's, dbEST)



https://www.ncbi.nlm.nih.gov/nuccore/

NCBI: Derivative Databases

Nucleotide derived
- Example: RefSeq, GENE

Protein-derived
- Example: CDD

Structure-derived
- Example: Structure

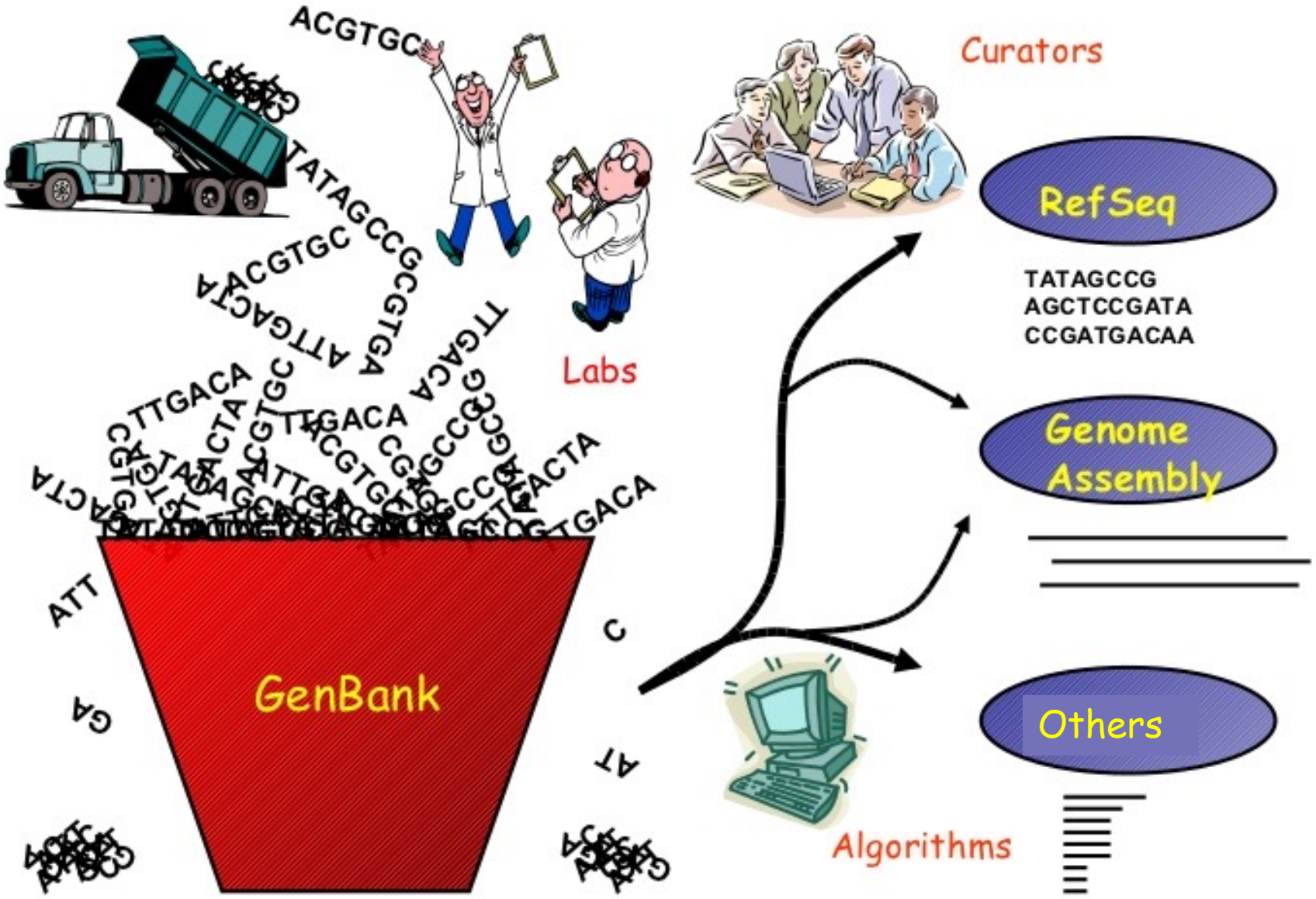
Human curated, compilation and correction of data
- Example: RefSeq

Computationally Derived
- Example: UniGene

Combinations
- Example: NCBI Genome Assembly

https://www.ncbi.nlm.nih.gov/refseq/

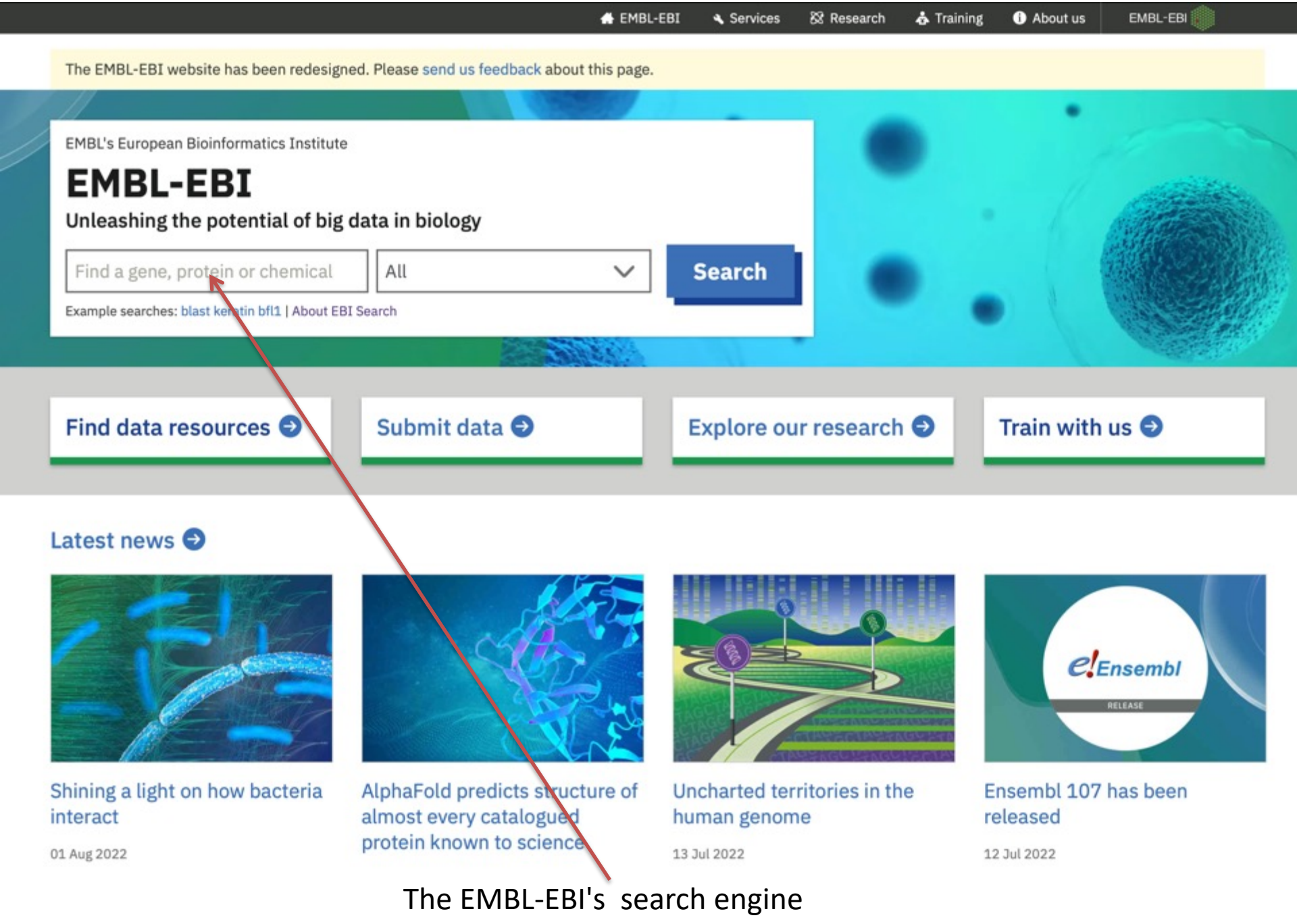
NCBI: Derivative Databases



https://www.slideshare.net/KavisaGhosh/ncbi

The EMBL-EBI

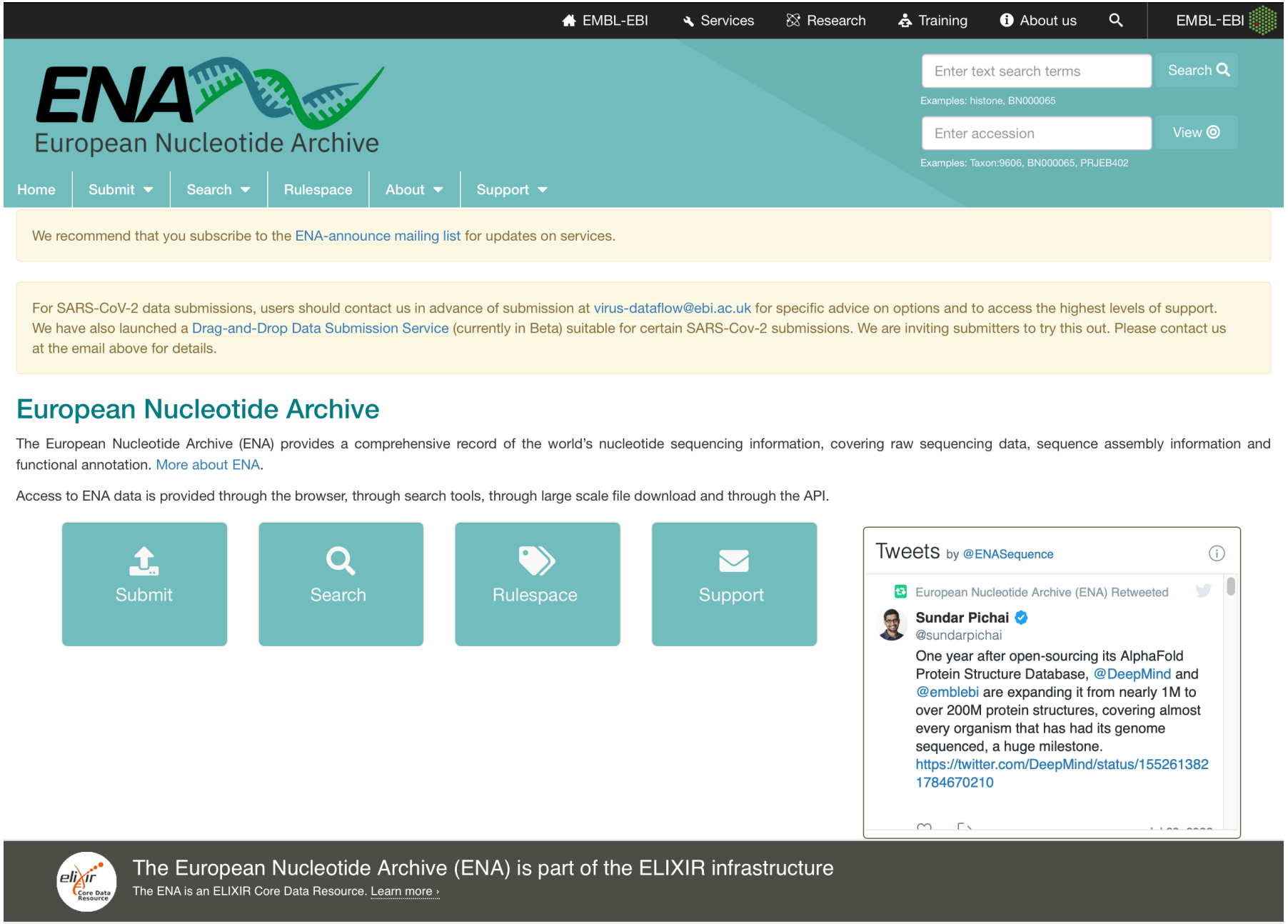
http://www.ebi.ac.uk/



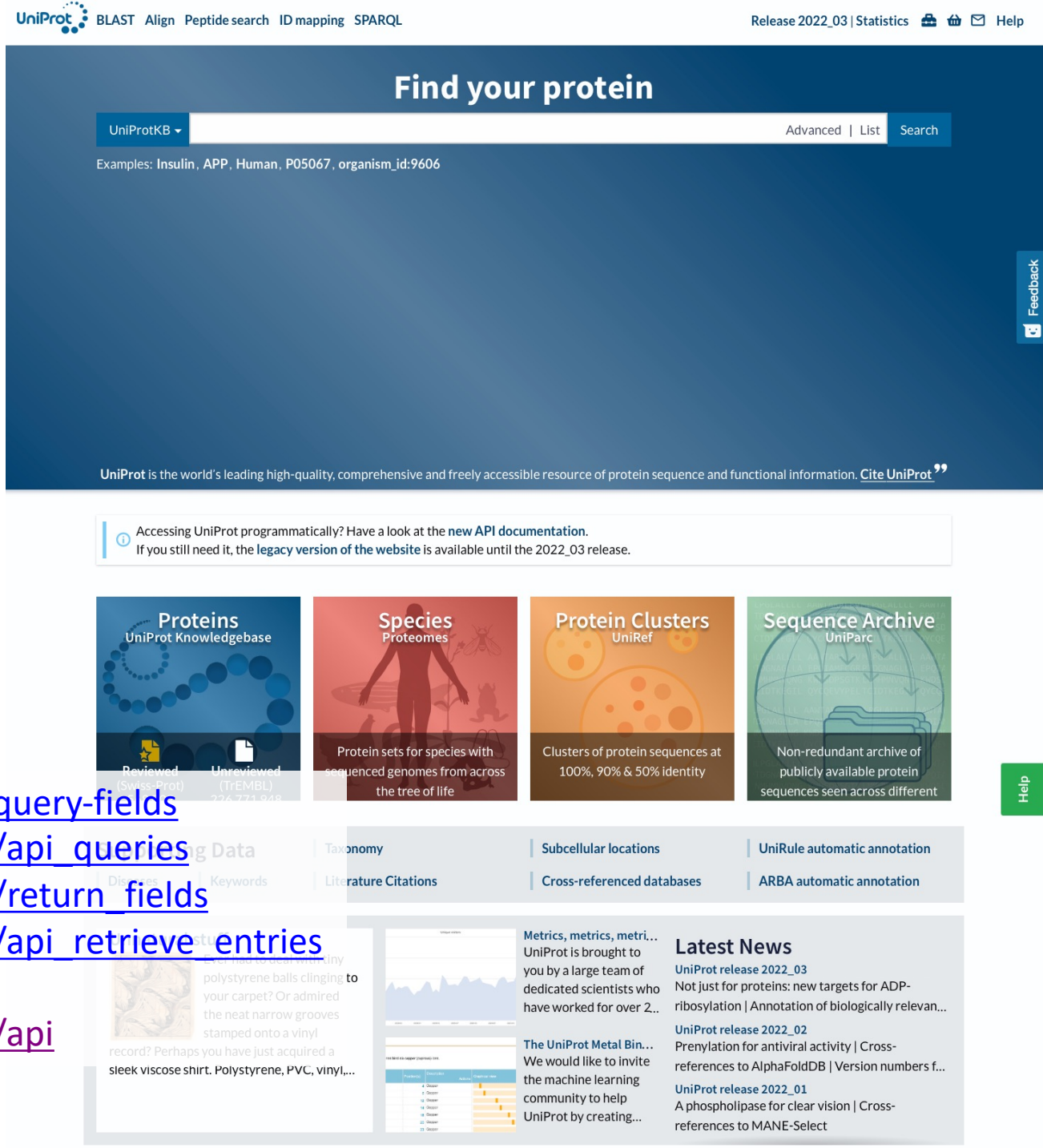
The EMBL-EBI's search engine

The EMBL-EBI nucleotide repository:ENA

http://www.ebi.ac.uk/ena/

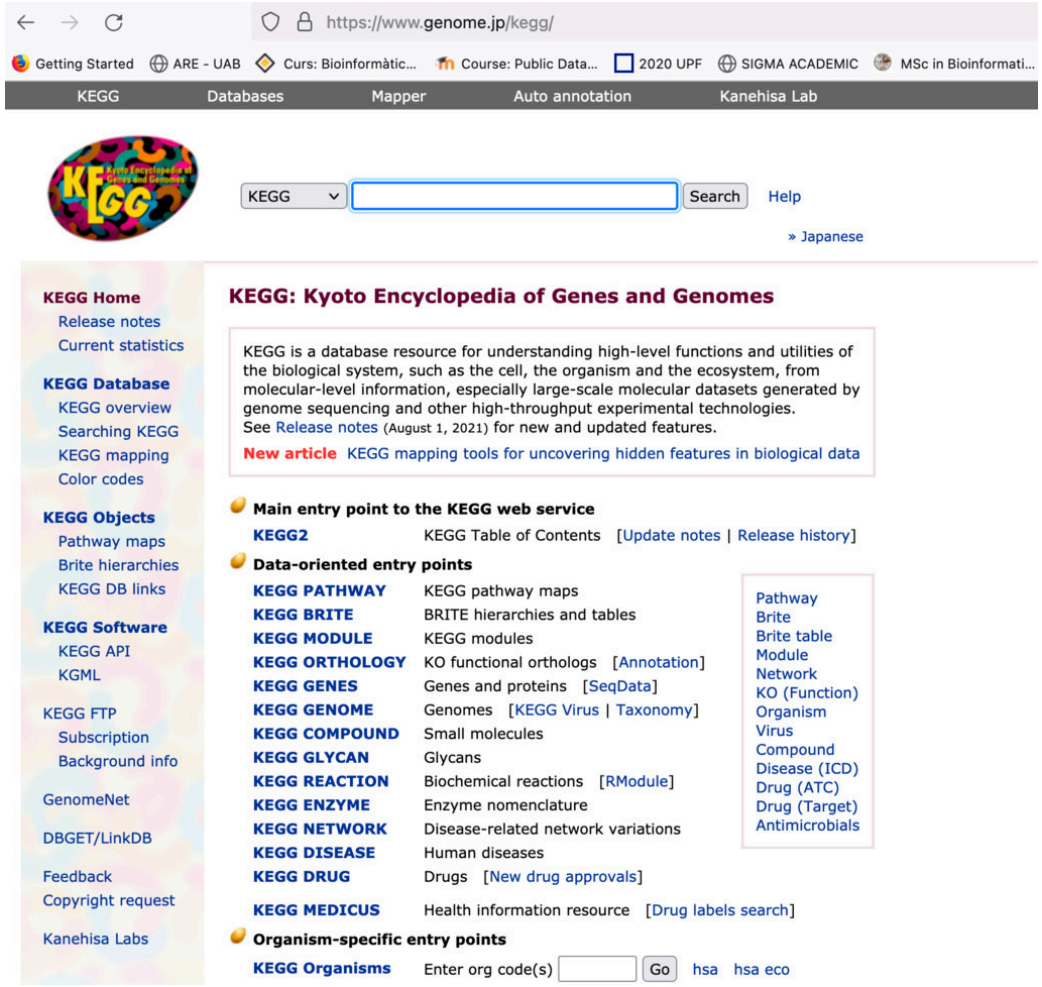


The mission of **UniProt** is to provide the scientific community with a comprehensive, high quality and freely accessible resource of protein sequence and functional information.



http://www.uniprot.org/

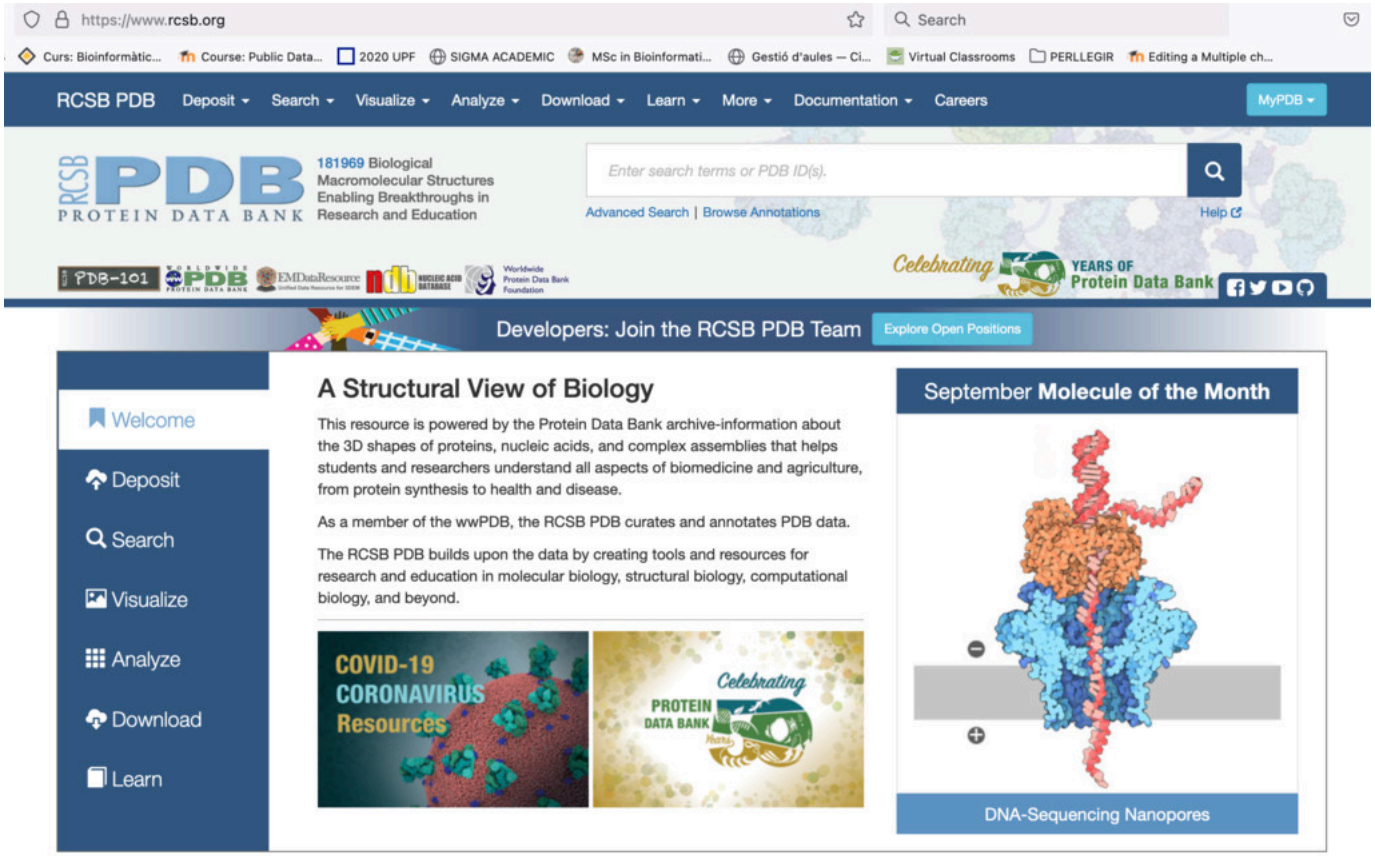
REST Web services access:
http://www.uniprot.org/help/query-fields
https://www.uniprot.org/help/api_queries
https://www.uniprot.org/help/return_fields
https://www.uniprot.org/help/api_retrieve_entries
If you want more:
https://www.uniprot.org/help/api



https://www.genome.jp/kegg/

REST API:

https://www.kegg.jp/kegg/rest/keggapi.html



https://www.rcsb.org/

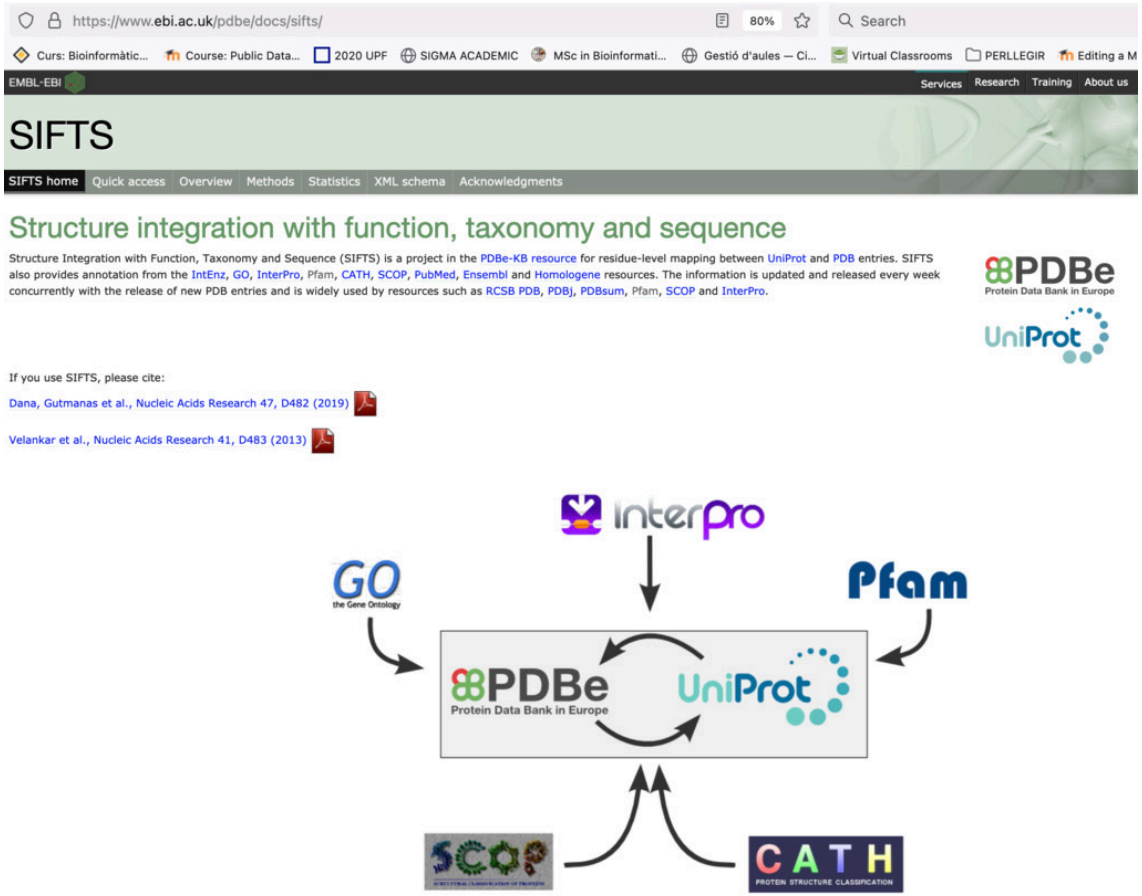
Web services

https://www.rcsb.org/docs/programmatic-access/web-services-overview

Doc: https://data.rcsb.org/redoc/index.html

Data API tutorial:https://data.rcsb.org/index.html

Search API tutorial:https://search.rcsb.org/index.html



https://www.ebi.ac.uk/pdbe/docs/sifts/
https://www.ebi.ac.uk/pdbe/docs/sifts/overview.html
REST API: http://www.ebi.ac.uk/pdbe/api/doc/sifts.html