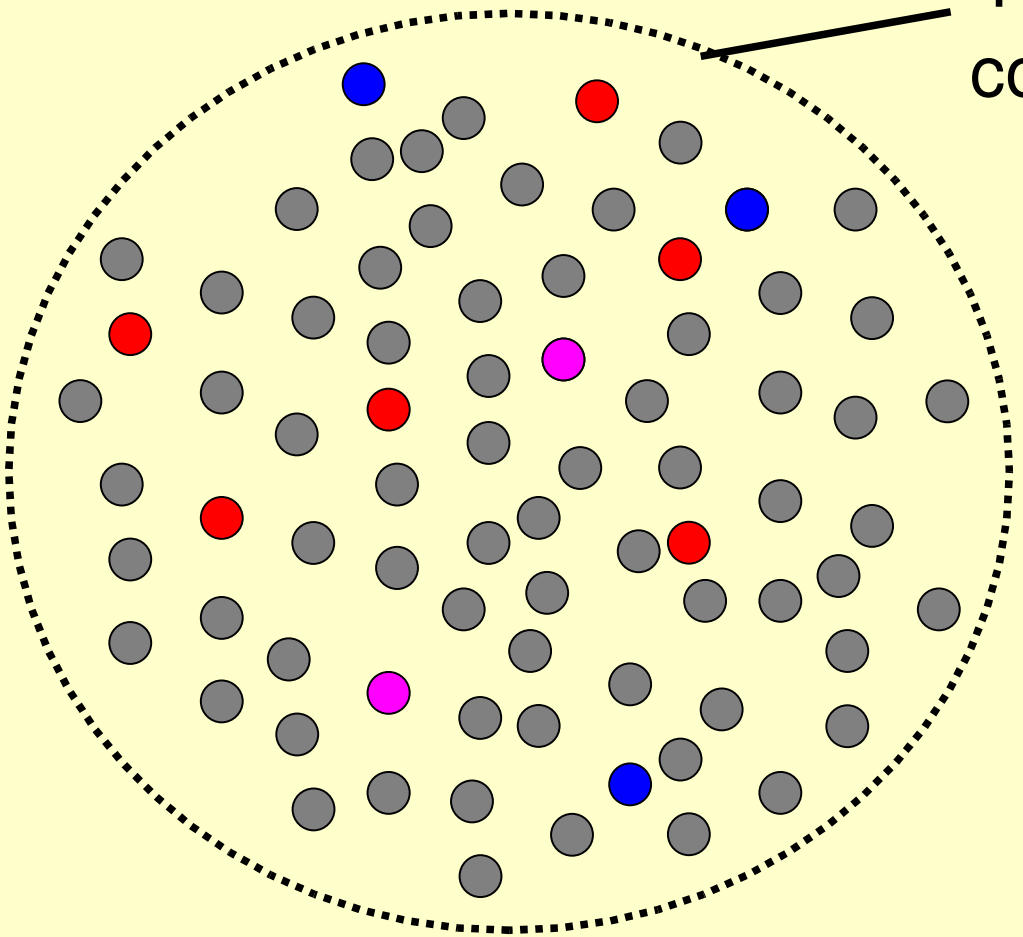
Identificación de Dominios de Proteínas

Escuela Complutense de Verano 2007

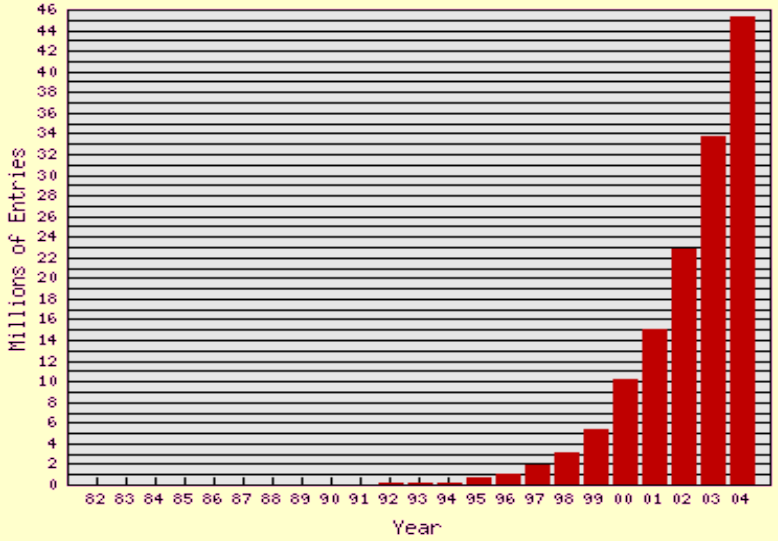
Luis Sánchez Pulido
Centro Nacional de Biotecnología
Madrid

¿Por qué analizamos secuencias?

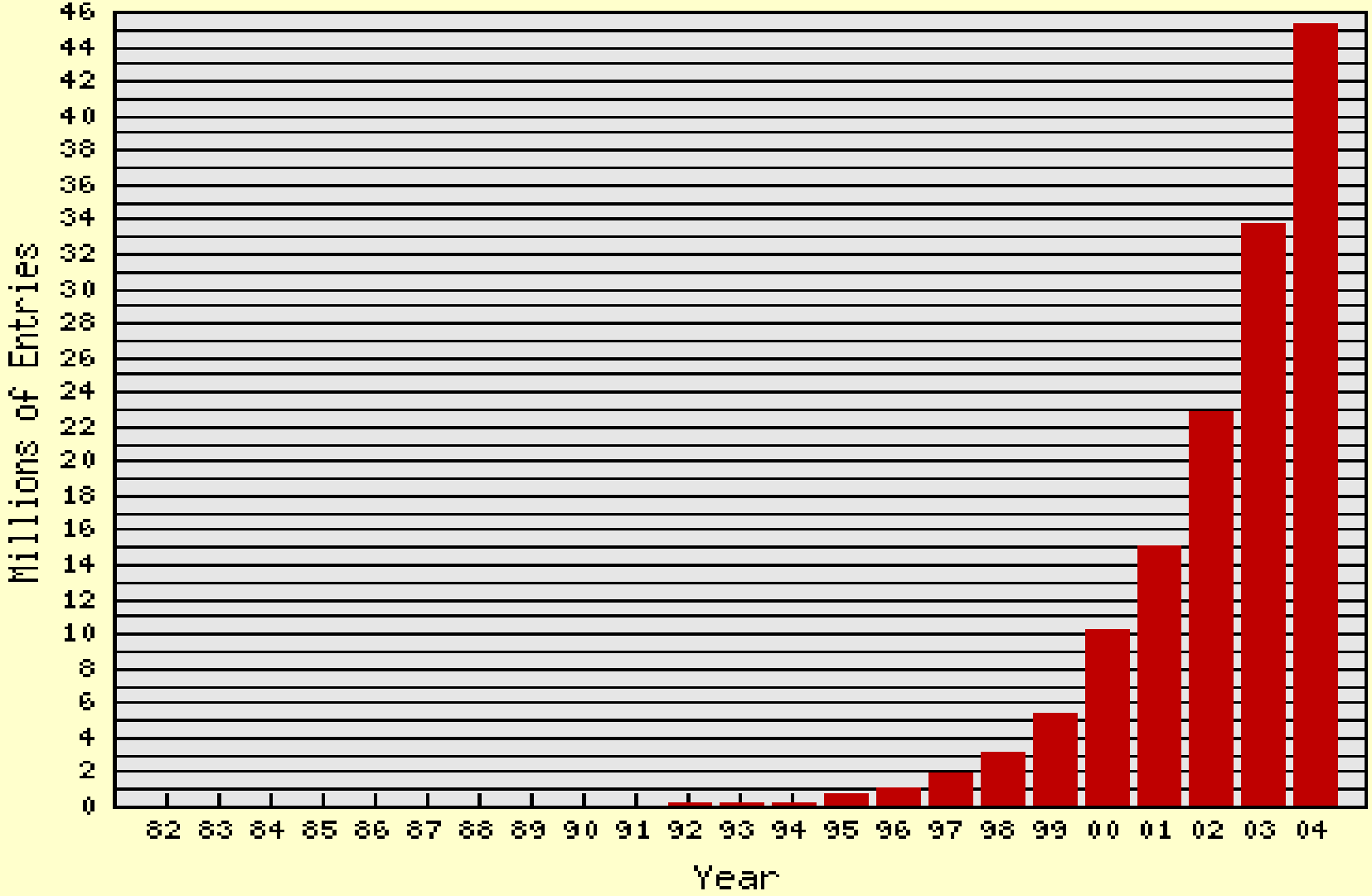


Proteínas de Secuencia conocida

- 3D
- Función
- Ambas
- ?????



¡¡¡ ESTAMOS DESBORDADOS !!!



Crecimiento de las bases de datos de secuencias.

Tomado de www3.ebi.ac.uk/Services/DBStats/

Gracias a la identificación de homología entre proteínas, podemos

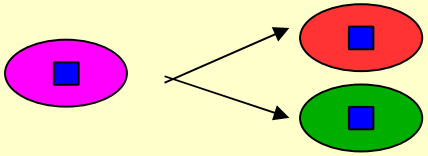
TRANSFERIR INFORMACIÓN

Estructural y/o Funcional

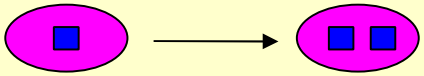
Homólogos: par de proteínas con un ancestro común.

...y dependiendo del motivo de su divergencia:

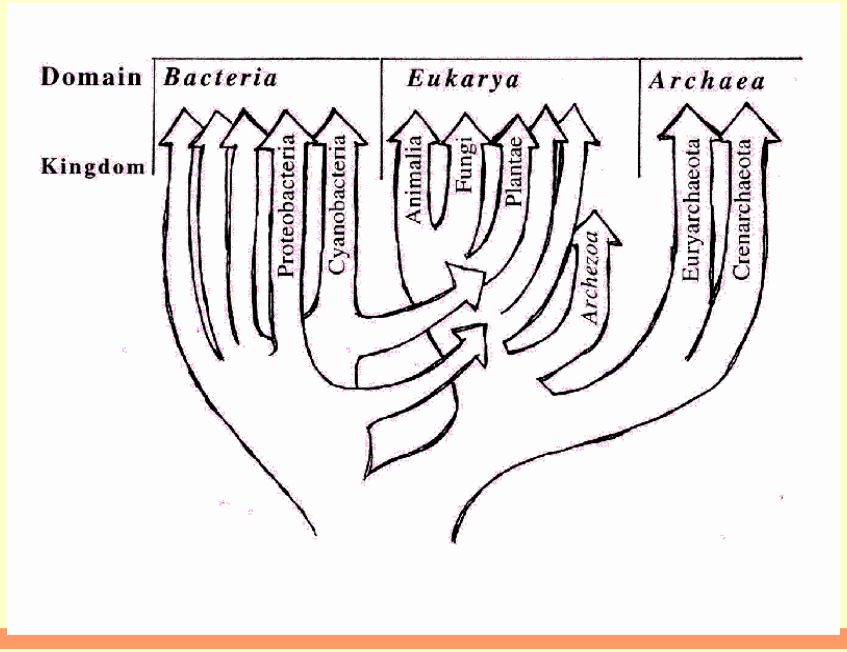
- **ortólogos** - especiación

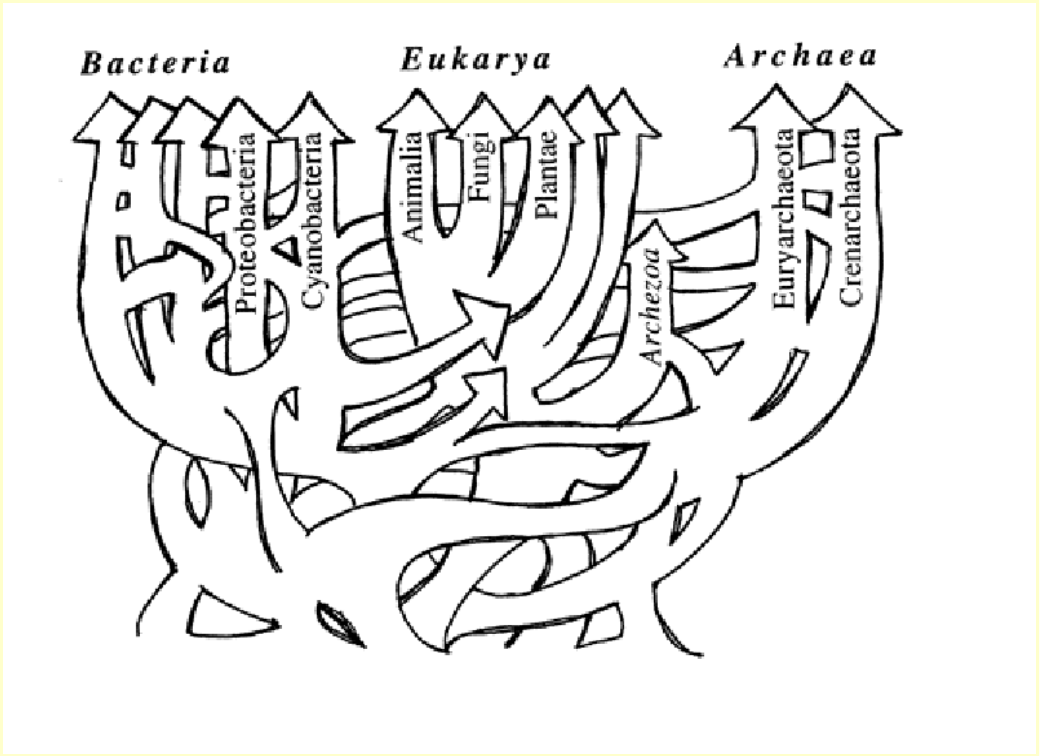


- **parálogos** – duplicación génica



- **xenólogos** – transferencia horizontal

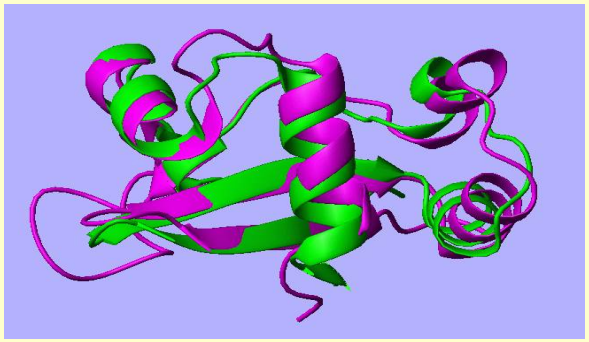




TRANSFERIR INFORMACIÓN

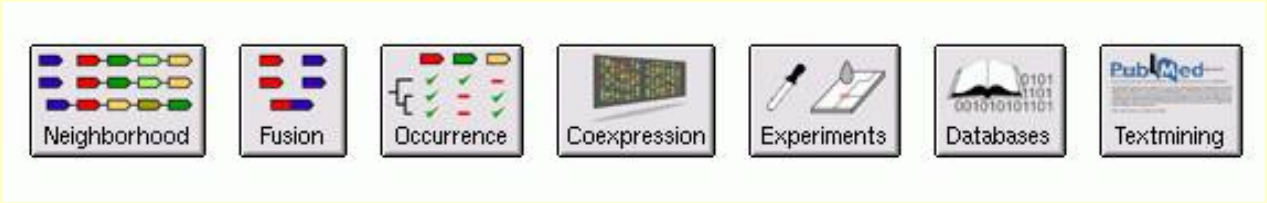
•*Estructural*

a partir de proteínas HOMÓLOGAS de estructura conocida por RayosX, RMN o ME

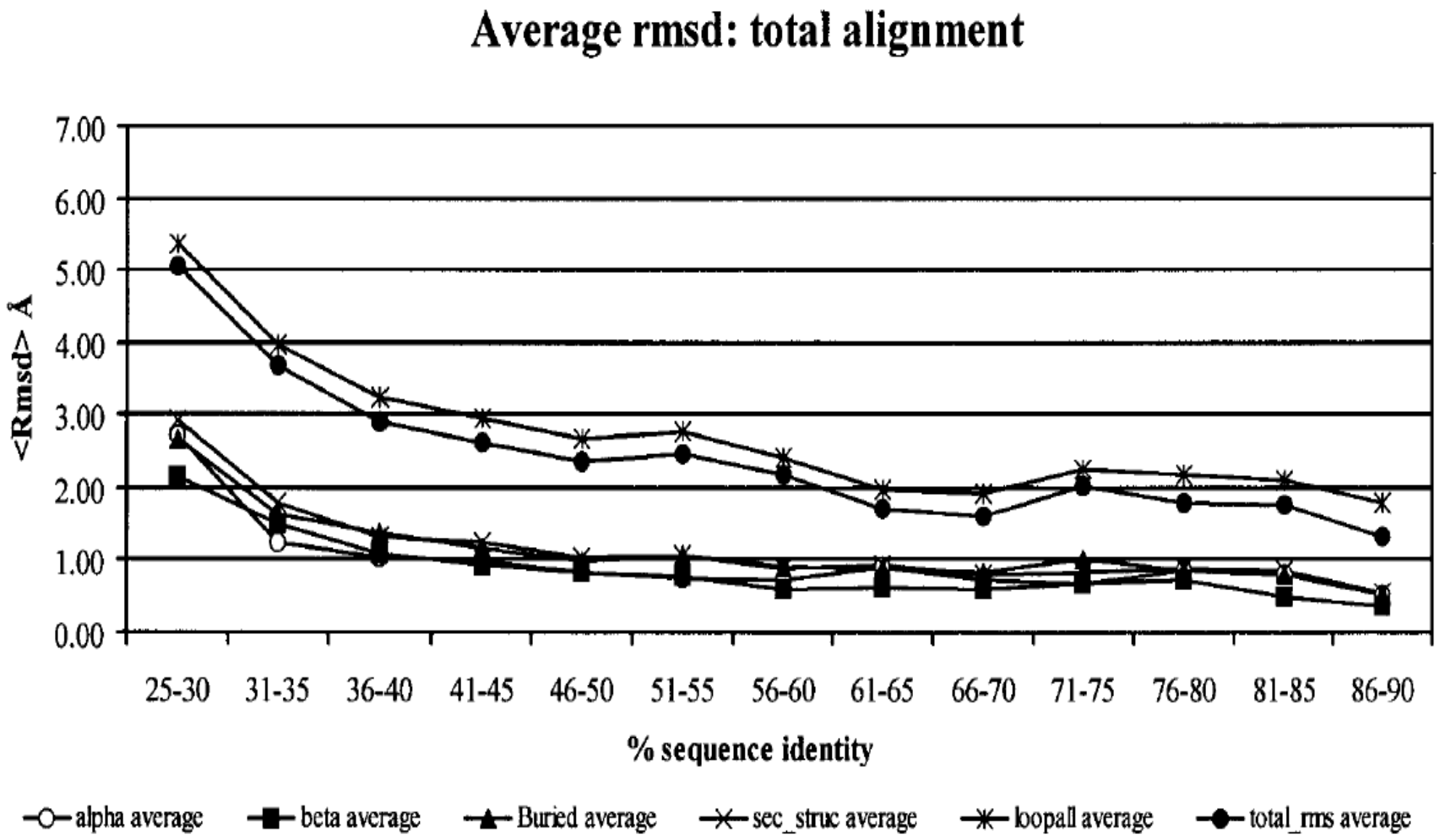


•*Funcional*

a partir de proteínas HOMÓLOGAS caracterizadas experimentalmente...
y su contexto genómico y proteómico.



La estructura se conserva mejor que la secuencia!

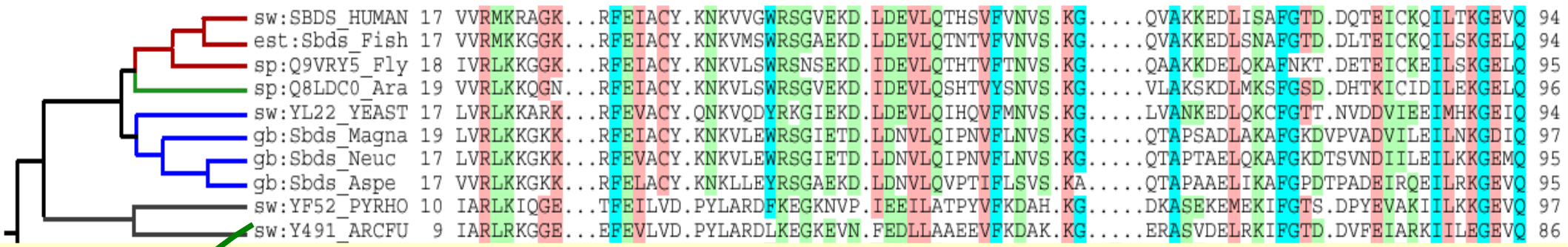


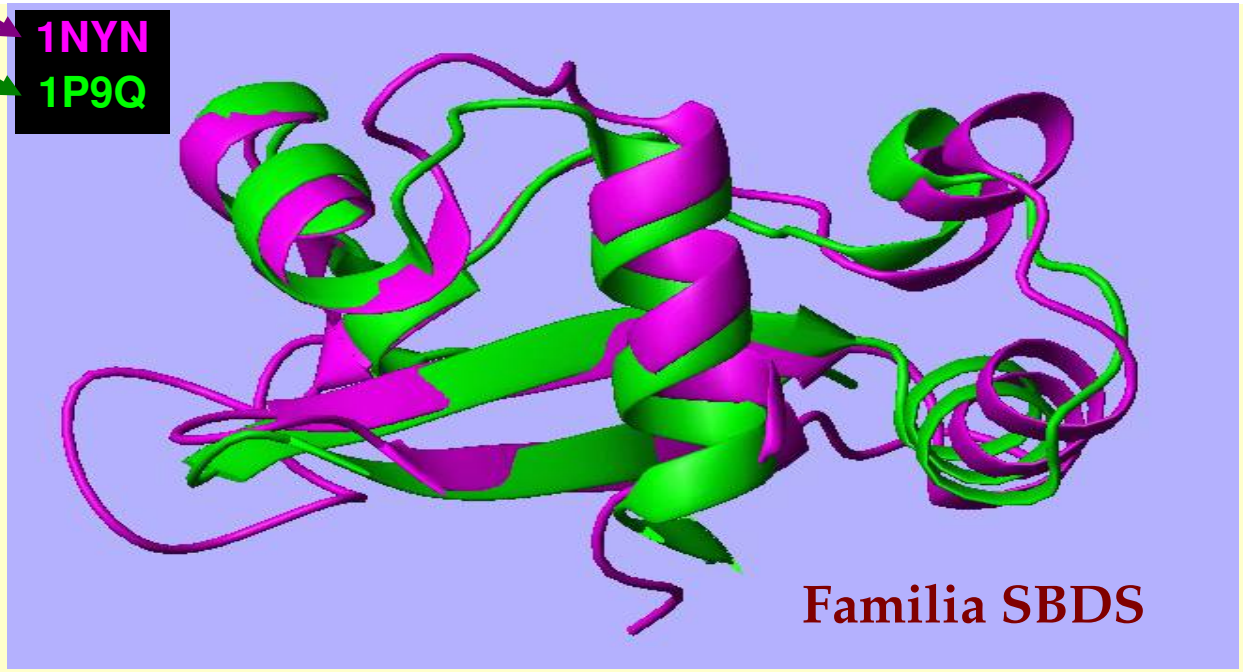
D'Alfonso G, Tramontano A, Lahm A.

Structural conservation in single-domain proteins: implications for homology modeling.

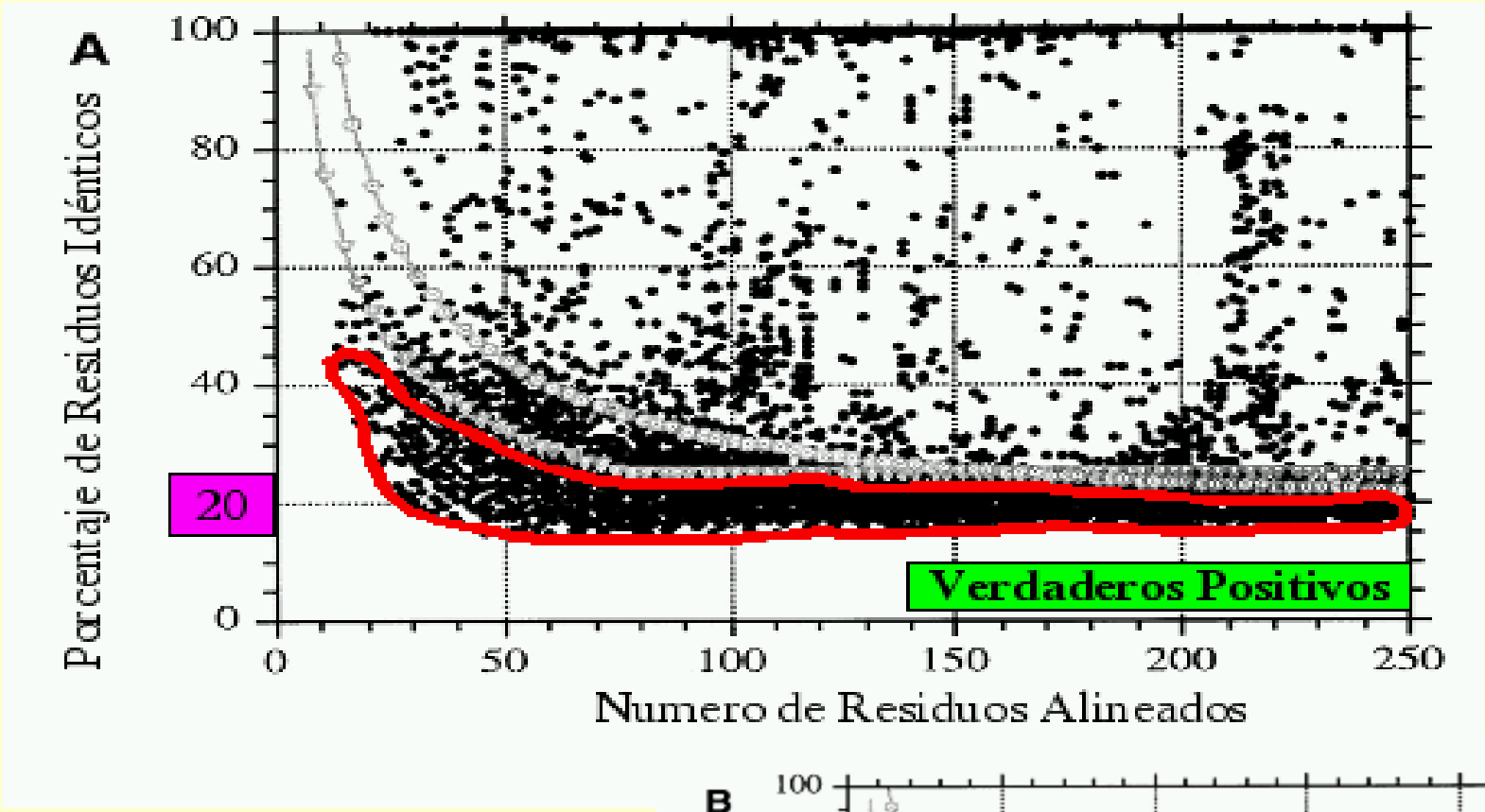
J Struct Biol. 134, 246-56. (2001)

A Remote Homology example:

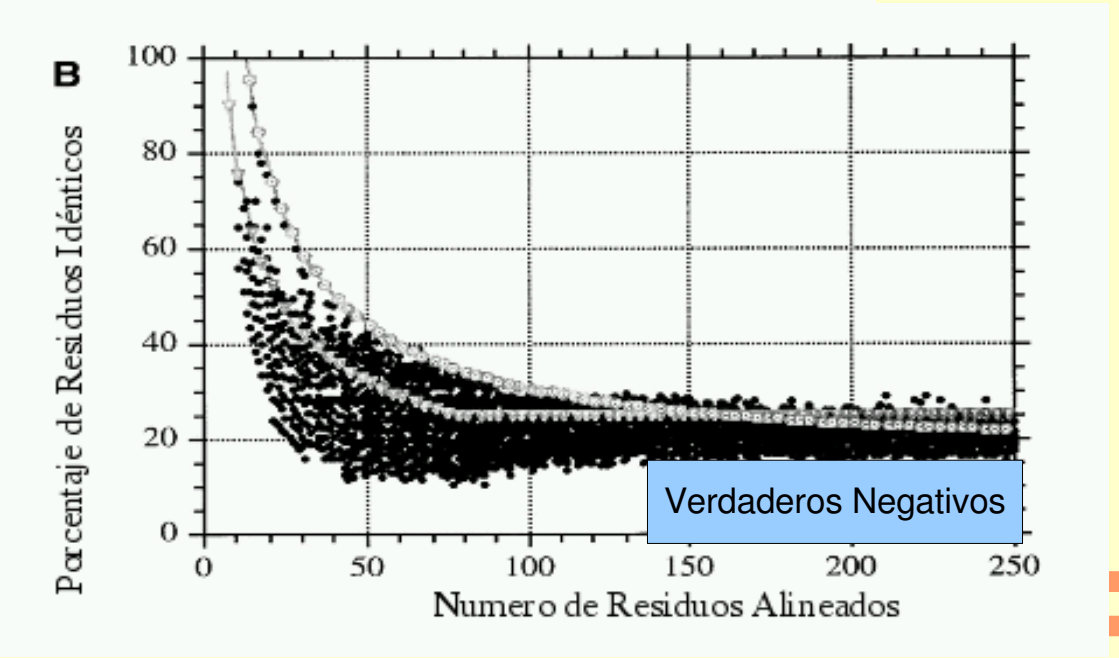




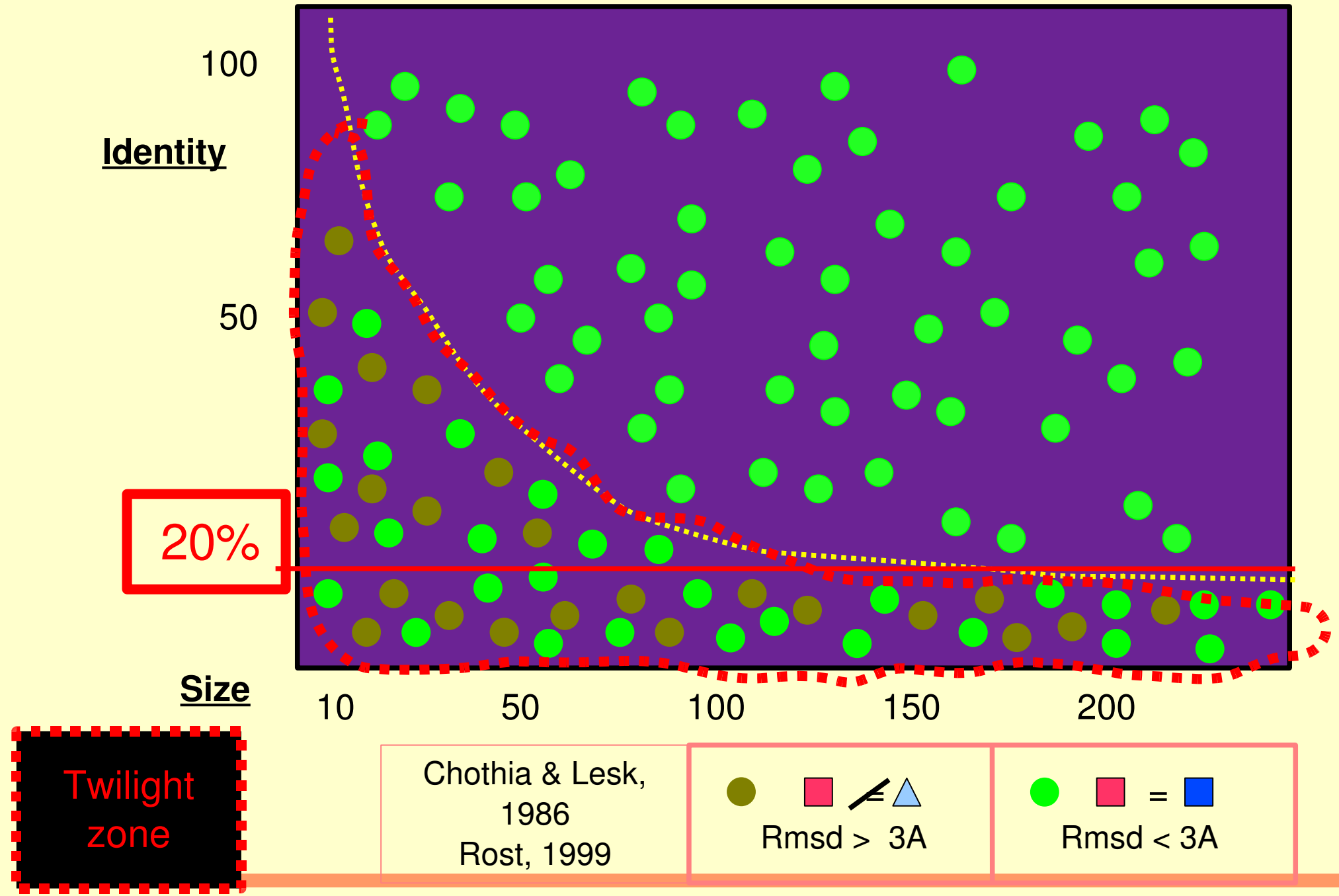
Definiendo Homología Remota



Rost B. (1999)
Twilight zone of
protein sequence alignments.
Protein Eng. 12:85-94.



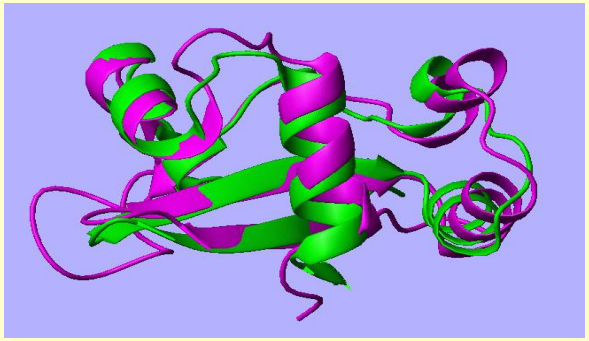
Comparisons between pairs of sequences with known structure



TRANSFERIR INFORMACIÓN

• *Estructural*

a partir de proteínas HOMÓLOGAS de estructura conocida por RayosX, RMN o ME



• *Funcional*

a partir de proteínas HOMÓLOGAS caracterizadas experimentalmente... y su contexto genómico y proteómico.

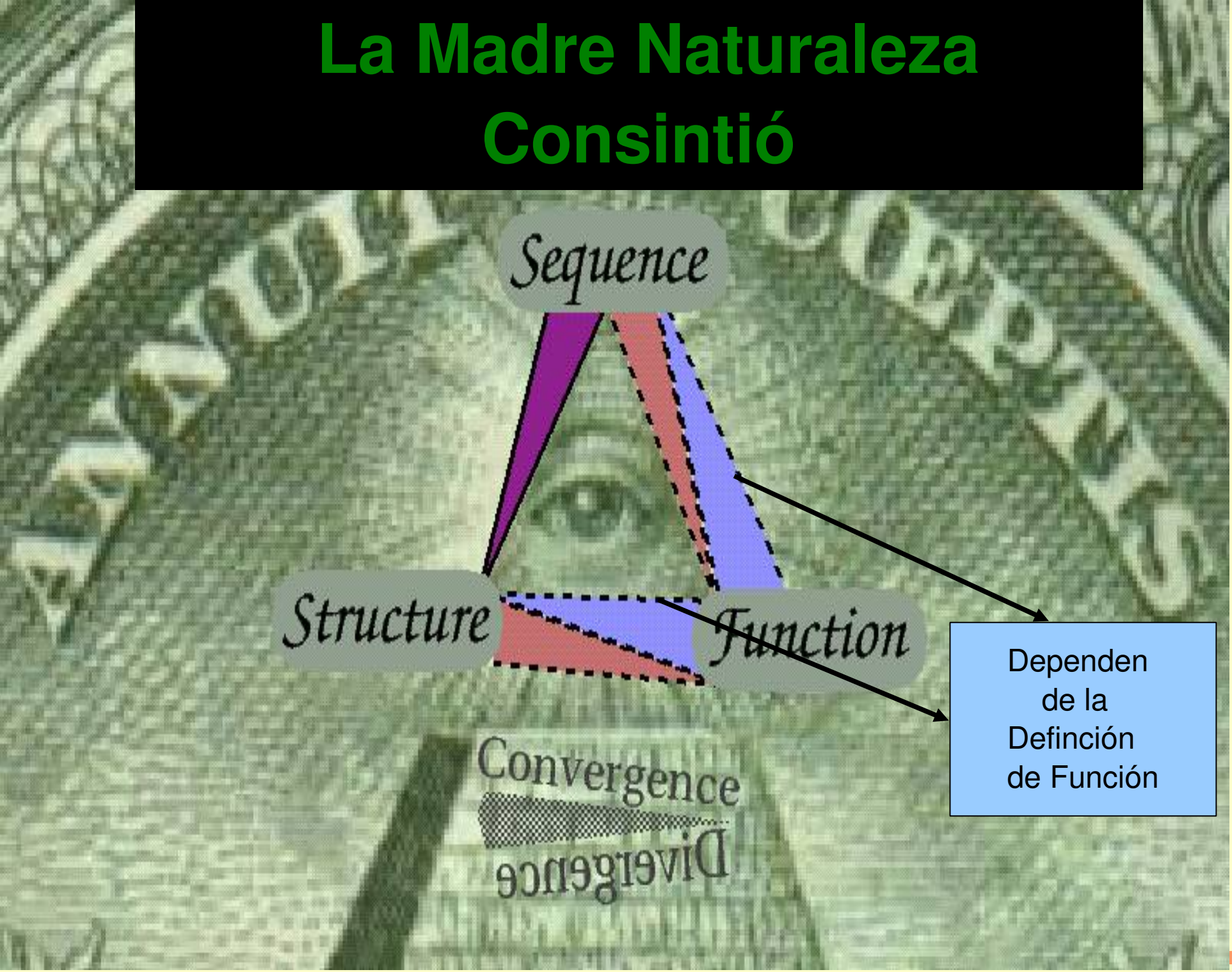
¿FUNCTION?

They are homologous Proteins...

The Function could be very divergent

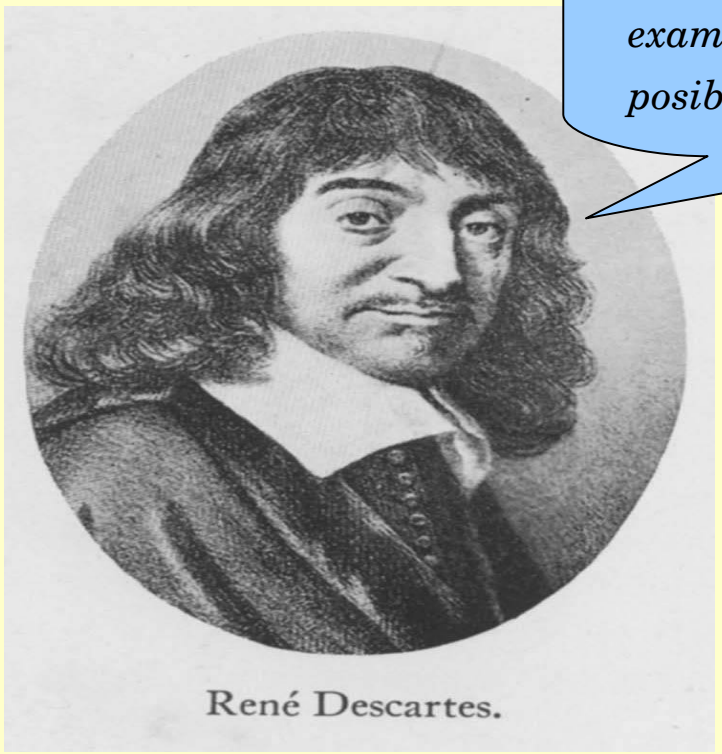
But... All of them bind GTP

La Madre Naturaleza Consintió

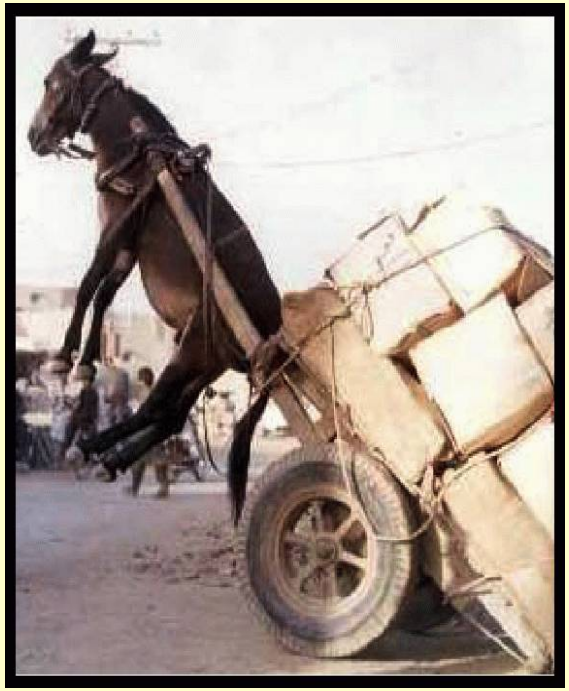


Tarea Compleja la de transferir información estructural y/o funcional entre proteínas homólogas.

Qué Hacemos??

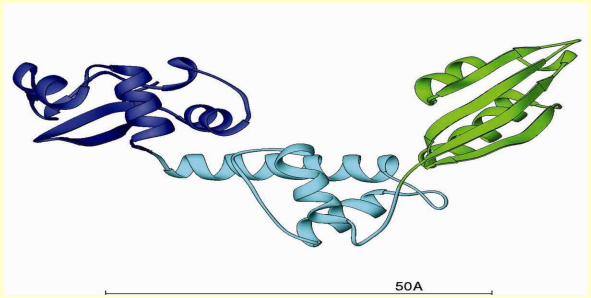


Dividir cada una de las dificultades a examinar, en tantas partes como sea posible y necesario para resolverlas mejor

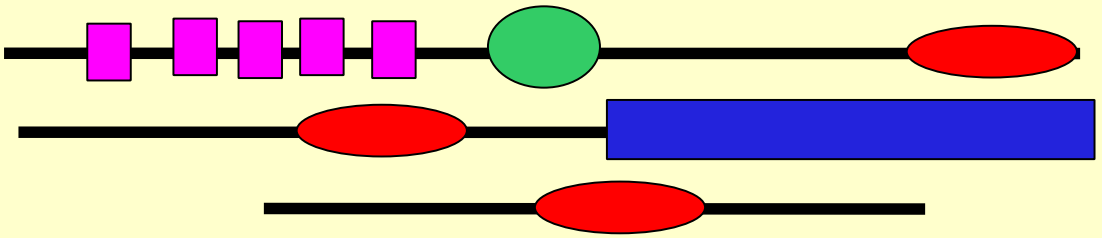


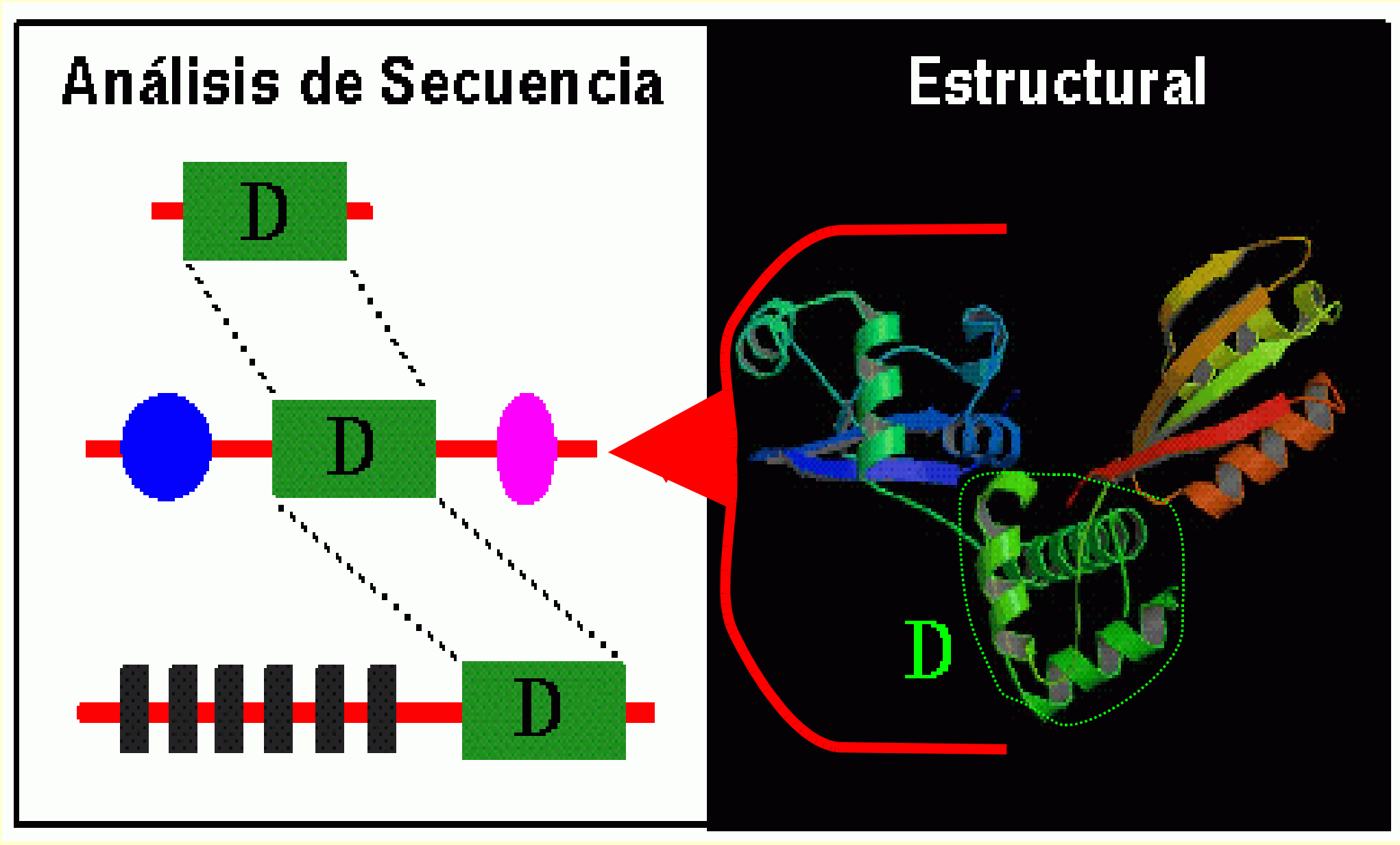
DEFINICIÓN DE DOMINIO

Los dominios de proteínas han sido descritos, **desde un punto de vista estructural**, como unidades estructurales compactas y localmente independientes, caracterizadas usualmente por un núcleo hidrofóbico bien definido.

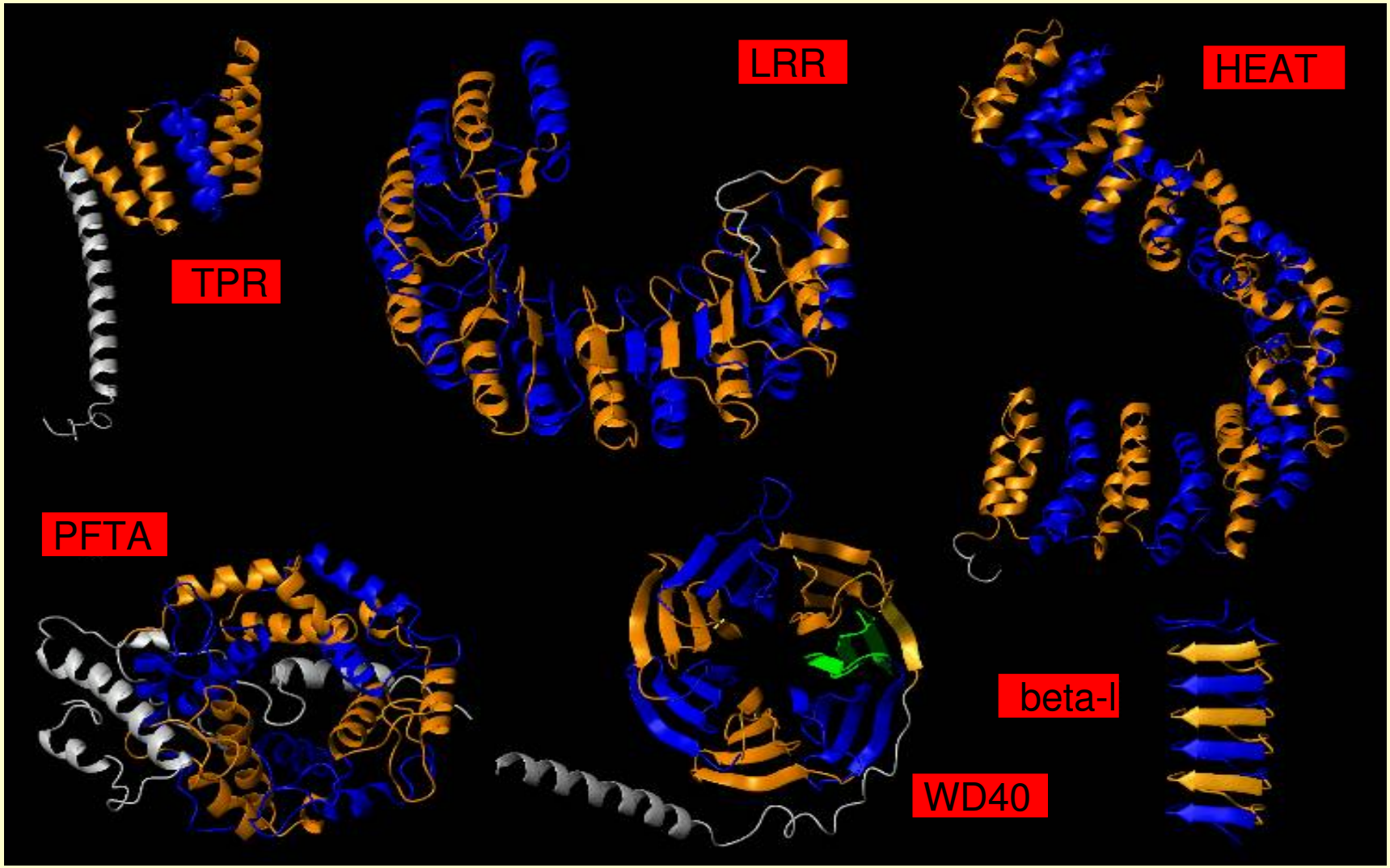


Desde el punto de vista del análisis de secuencia, los dominios se definen como regiones conservadas evolutivamente y adquieren mayor relevancia si son descritos como módulos móviles, es decir, presentes en diferentes familias de proteínas de arquitectura diversa.




Análisis de Secuencia
Estructural
D
D
D
D

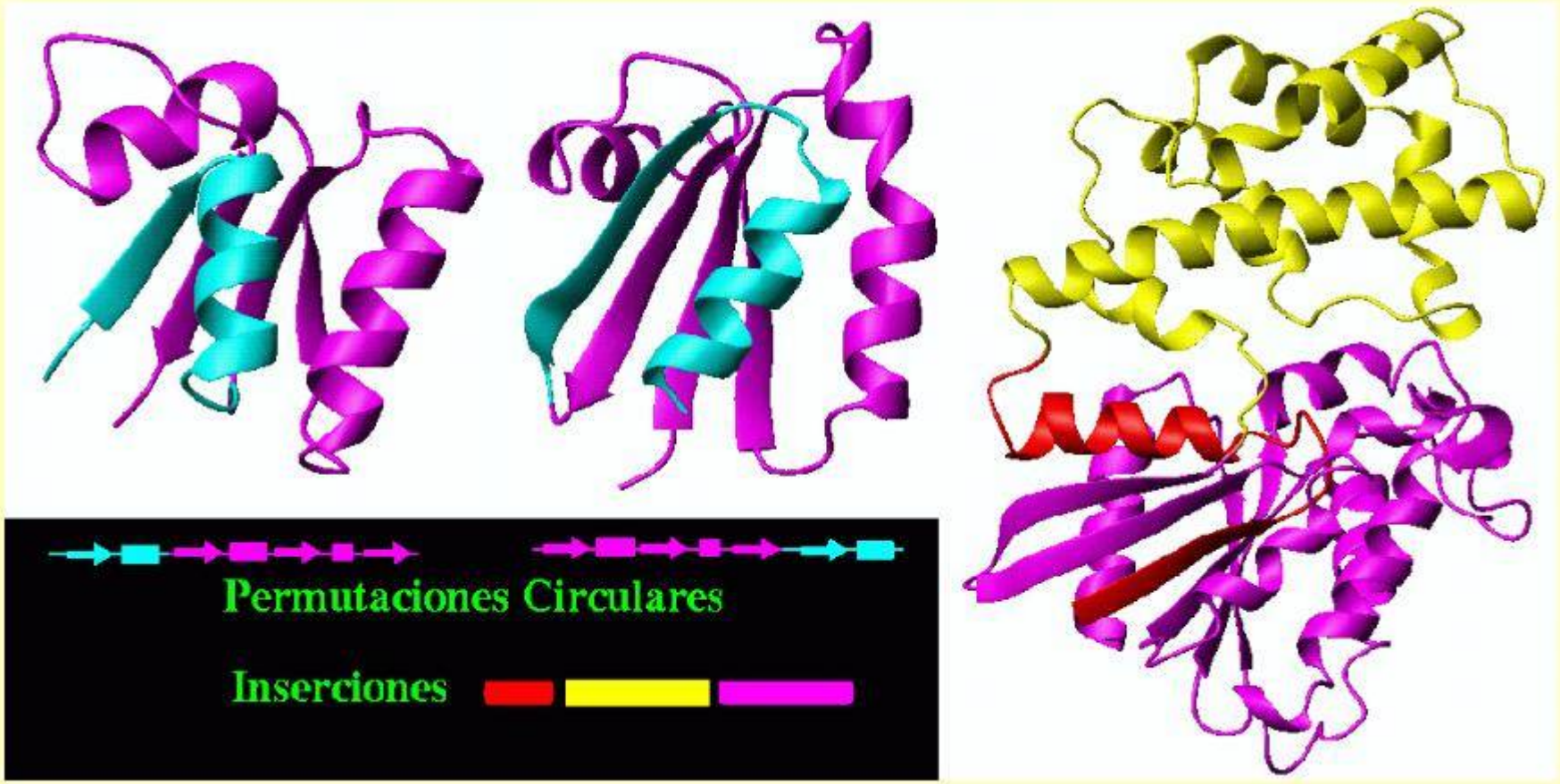
REPEATS – In the limits of Domain Definition



Protein repeats. Short specialist review for the Encyclopedia of Genomics, Proteomics, and
Cedida por: Perez-Iratxeta C, Andrade MA (2005) Bioinf. Ed. Wiley and Sons Ltd., UK.

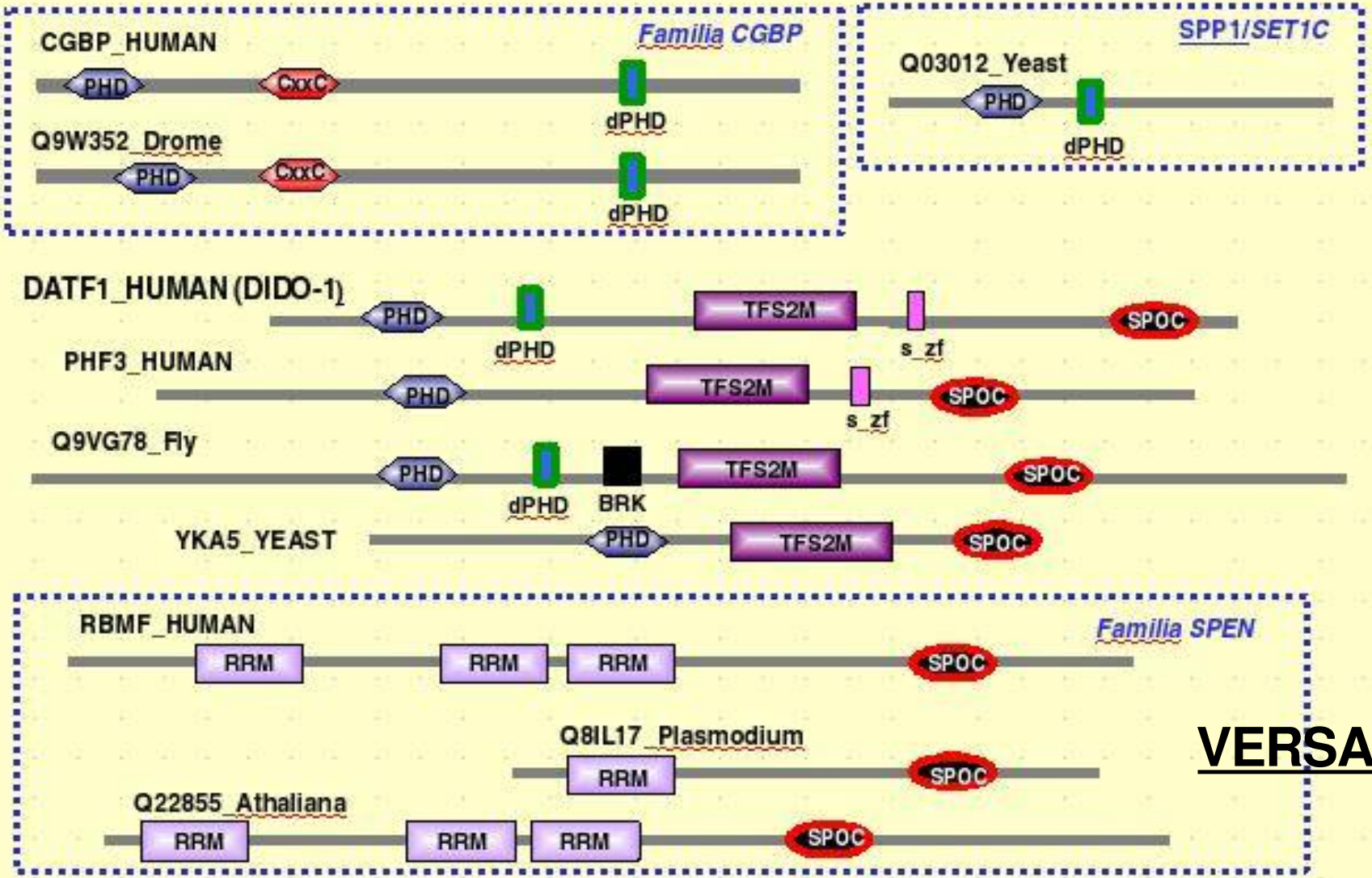
- **Protein irregularities that hinder sequence analysis**
- **Low complexity regions**
- **Repeats, Trans-membrane and Coiled-coil regions (high mutation rates)**
- **and Fold irregularities, such as:**

  Circular Permutations and Insertions



The role of domains in protein evolution

Shuffling, Accretion and Supra-Domains



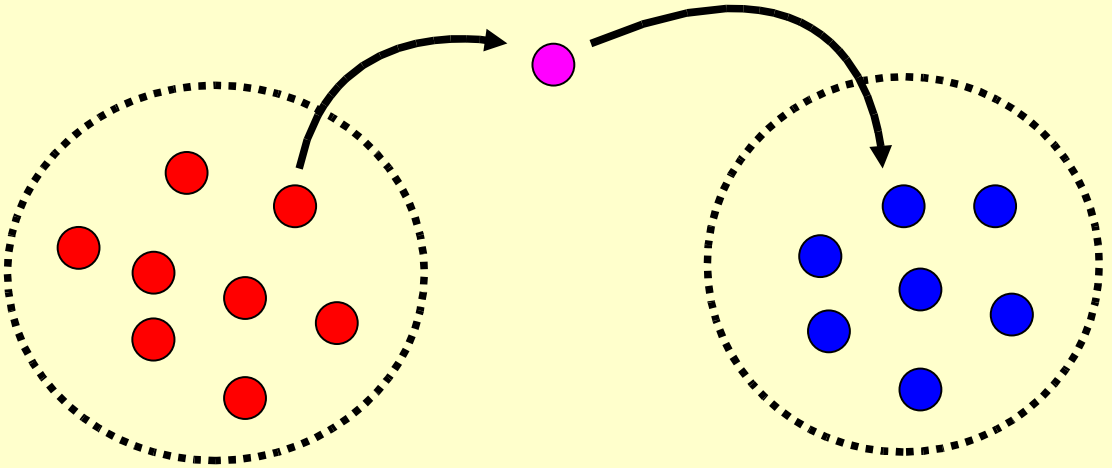
VERSATILITY !!

METHODS
ON
DOMAIN
ORIENTED
SEQUENCE ANALYSIS

Detection of homologous protein sequences

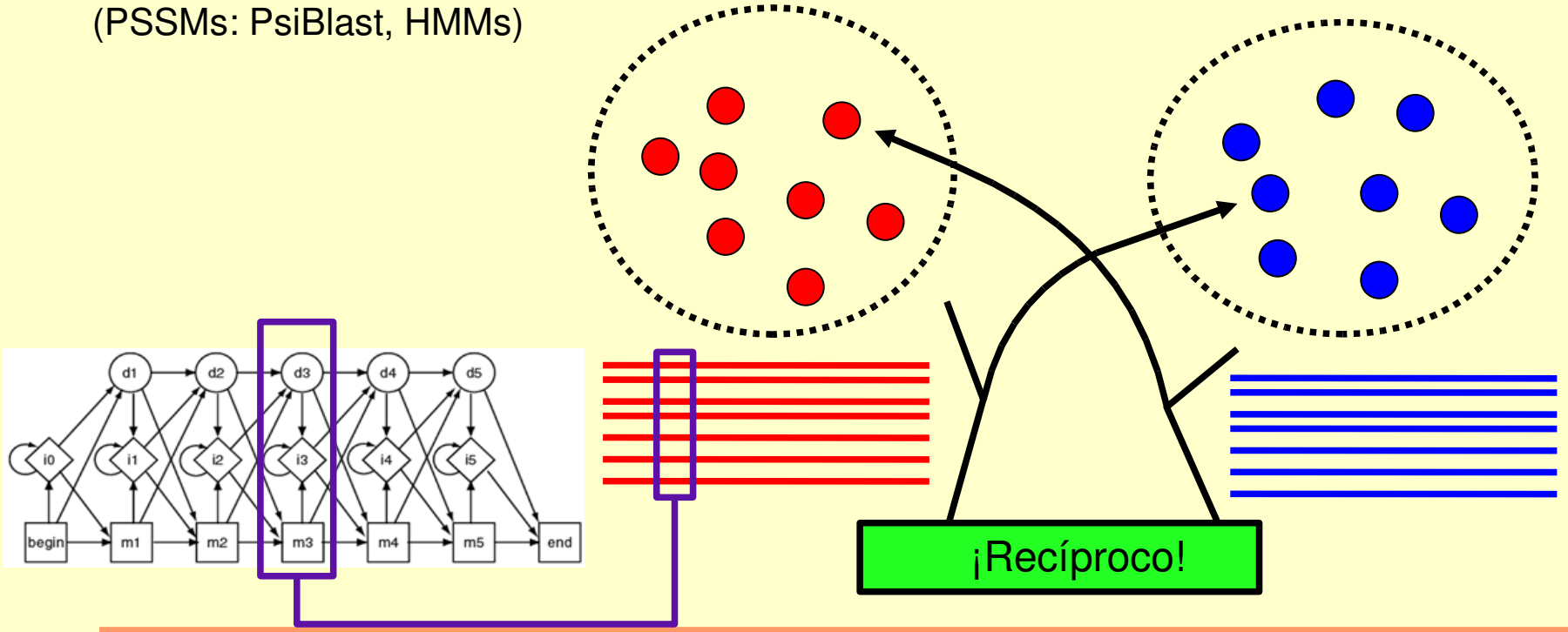
Two strategies

ISS (Blast, FASTA)



Profiles

(PSSMs: PsiBlast, HMMs)



Pfam: Pfam Home Page - Mozilla Firefox

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http://www.sanger.ac.uk/Software/Pfam/

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Pfam

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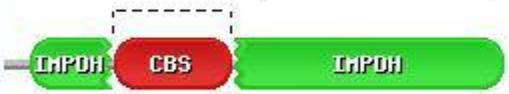
Search by:
- Protein name or sequence
- Keyword
- Domain query
- DNA sequence
- Taxonomy query

Pfam is a large collection of multiple seque s and hidden Markov models covering many common protein domains and famil mily in Pfam you can:

- Look at multiple alignments
- View protein domain architectures
- Examine species distribution
- Follow links to other databases
- View known protein structures

For more information on Pfam, on using this site, or on the changes between Pfam releases 19.0 and 20.0, click here.

Pfam can be used to view the domain organisation of proteins. A typical example is shown below. Notice that a single protein can belong to several Pfam families.



74% of protein sequences have at least one match to Pfam. This number is called the sequence coverage and is shown in the pie chart on the right.

Pfam is a database of two parts, the first is the curated part of Pfam containing over 8296 protein families. To give Pfam a more comprehensive coverage of known proteins we automatically generate a supplement called Pfam-B. This contains a large number of small families taken from the PRODOM database that do not overlap with Pfam-A. Although of lower quality Pfam-B families can be useful when no Pfam-A families are found.

Version 20.0

May 2006, **8296** families

Sequence coverage Pfam-A : 74%
Sequence coverage Pfam-B : 11%
Other

Web feed

You can use the RSS feed to keep updated about Pfam releases

XML RSS

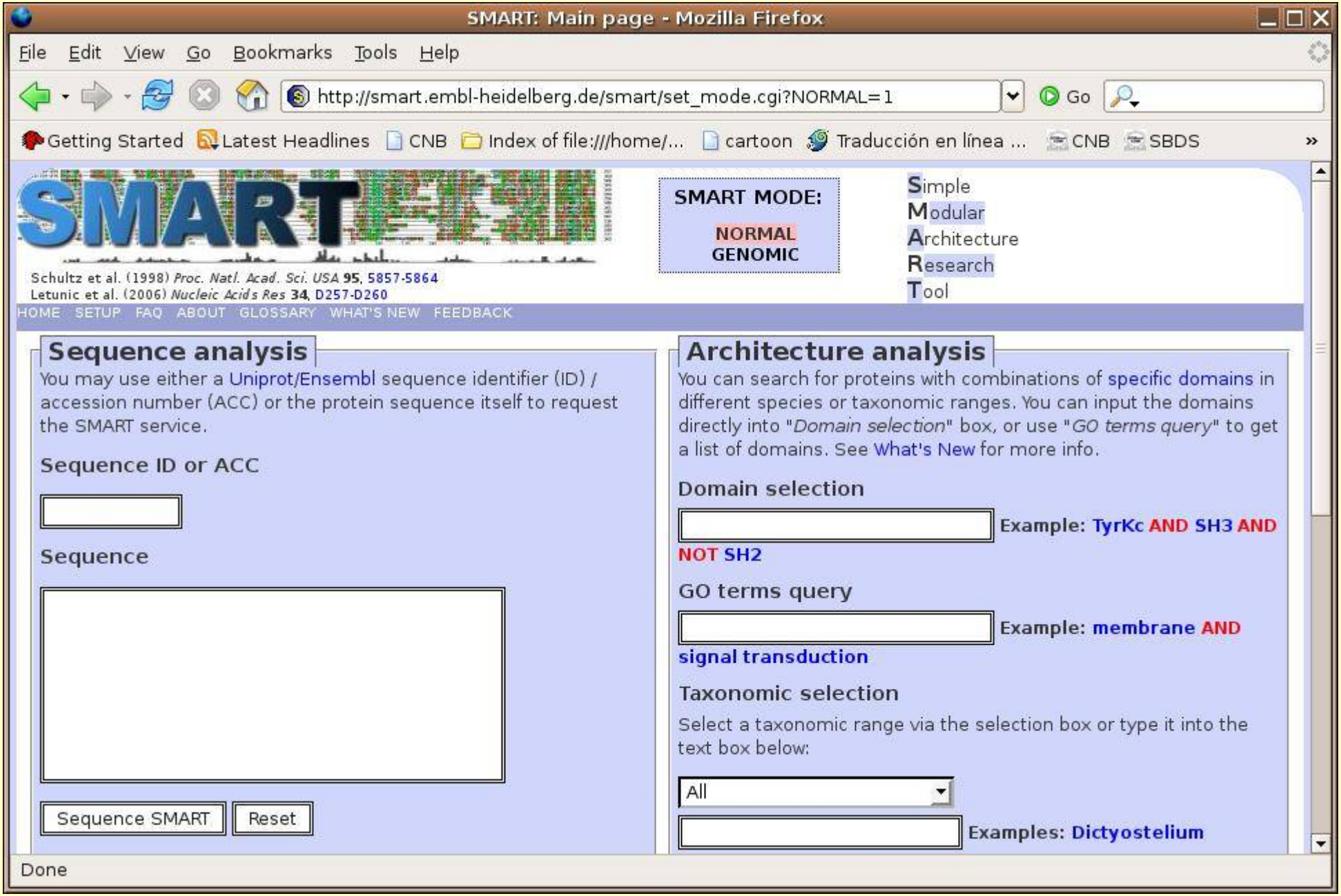
Enter your keyword(s) here

Go Example

Enter a SWISS-PROT 48.1 or TrEMBL 31.1 name or accession number

Go Example

Looking up www.sanger.ac.uk...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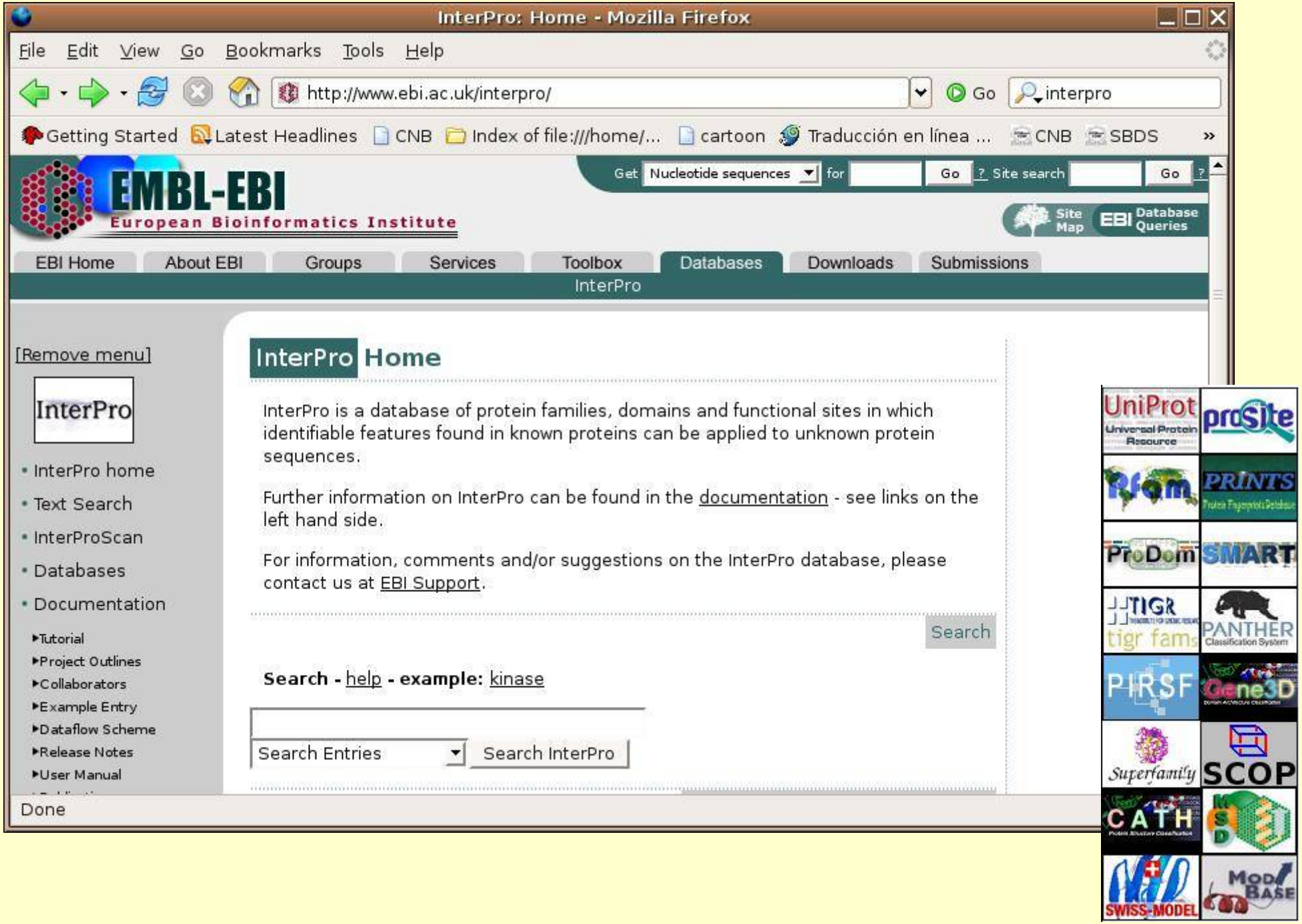
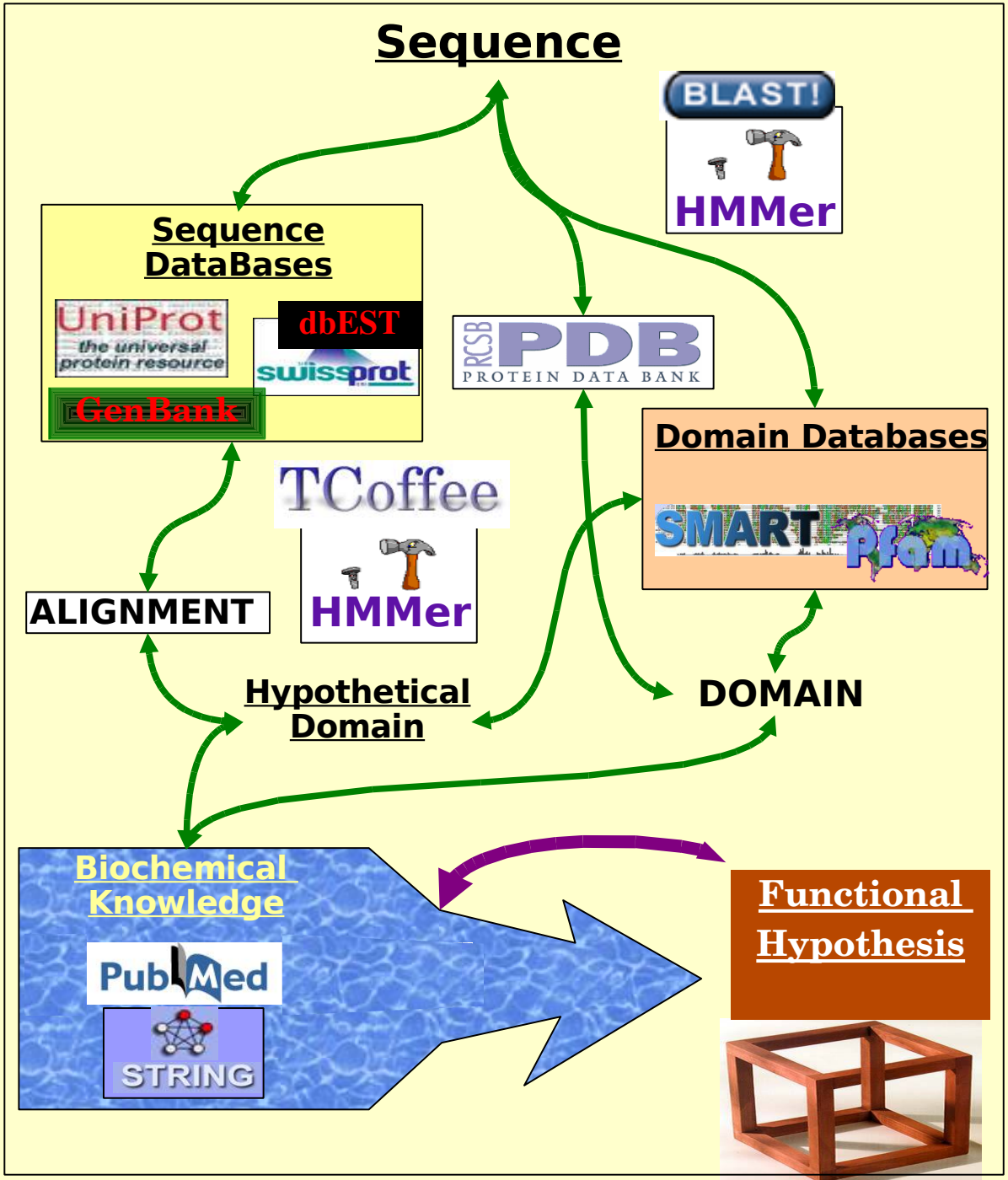
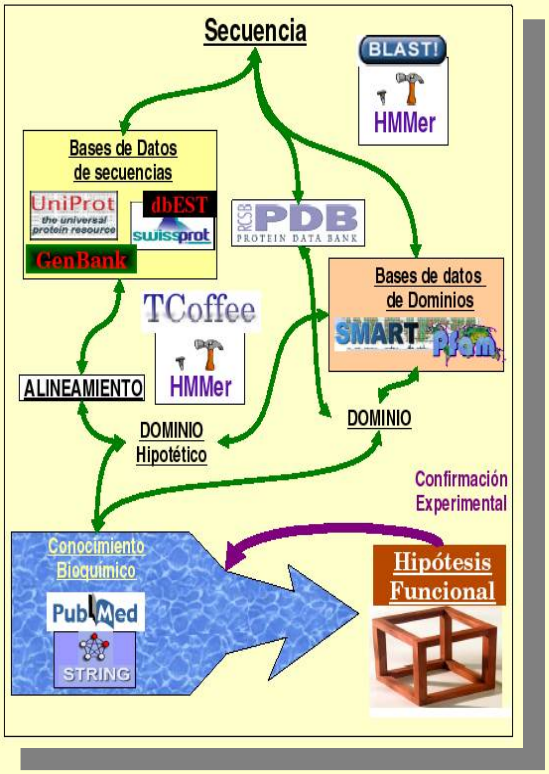
SMART
Schultz et al. (1998) Proc. Natl. Acad. Sci. USA 95, 5857-5864
Letunic et al. (2006) Nucleic Acids Res 34, D257-D260
SMART MODE:
NORMAL
GENOMIC
Simple
Modular
Architecture
Research
Tool
HOME SETUP FAQ ABOUT GLOSSARY WHAT'S NEW FEEDBACK
Sequence analysis
You may use either a Uniprot/Ensembl sequence identifier (ID) / accession number (ACC) or the protein sequence itself to request the SMART service.
Sequence ID or ACC
Sequence
Sequence SMART
Reset
Architecture analysis
You can search for proteins with combinations of specific domains in different species or taxonomic ranges. You can input the domains directly into "Domain selection" box, or use "GO terms query" to get a list of domains. See What's New for more info.
Domain selection
Example: TyrKc AND SH3 AND NOT SH2
GO terms query
Example: membrane AND signal transduction
Taxonomic selection
Select a taxonomic range via the selection box or type it into the text box below:
All
Examples: Dictyostelium
Done

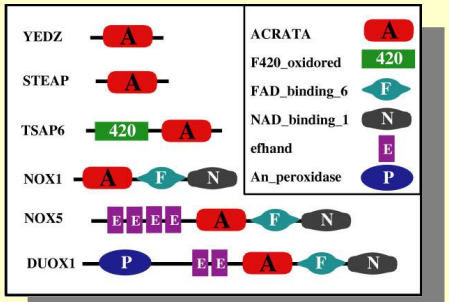

InterPro: Home - Mozilla Firefox
File Edit View Go Bookmarks Tools Help
http://www.ebi.ac.uk/interpro/
Go
interpro
Getting Started
Latest Headlines
CNB
Index of file:///home/...
cartoon
Traducción en línea ...
CNB
SBDS
EMBL-EBI
European Bioinformatics Institute
Get Nucleotide sequences for Go ? Site search Go ?
Site Map
EBI Database Queries
EBI Home
About EBI
Groups
Services
Toolbox
Databases
Downloads
Submissions
InterPro
[Remove menu]
InterPro
InterPro home
Text Search
InterProScan
Databases
Documentation
Tutorial
Project Outlines
Collaborators
Example Entry
Dataflow Scheme
Release Notes
User Manual
InterPro Home
InterPro is a database of protein families, domains and functional sites in which identifiable features found in known proteins can be applied to unknown protein sequences.
Further information on InterPro can be found in the documentation - see links on the left hand side.
For information, comments and/or suggestions on the InterPro database, please contact us at EBI Support.
Search
Search - help - example: kinase
Search Entries
Search InterPro
Done
UniProt
Universal Protein Resource
proSite
Pfam
PRINTS
ProDom
SMART
TIGR
tigr fams
PANTHER
Classification System
PIRSF
Gene3D
Superfamily
SCOP
CATH
MSD
SWISS-MODEL
ModBase

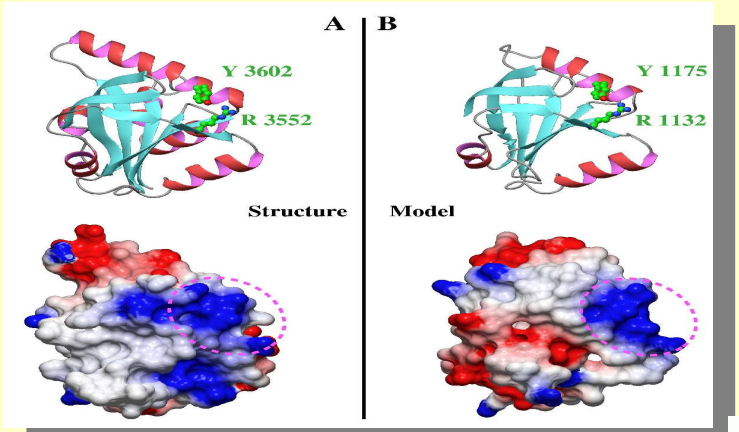
Domain Oriented Sequence Analysis Flow-Chart

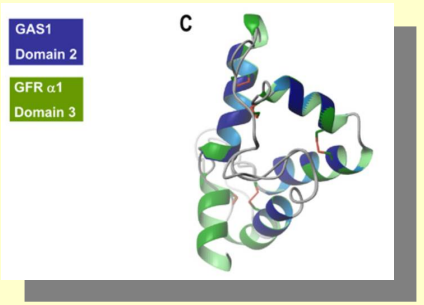


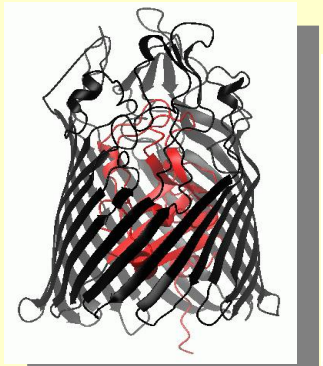
REAL-LIFE EXAMPLES

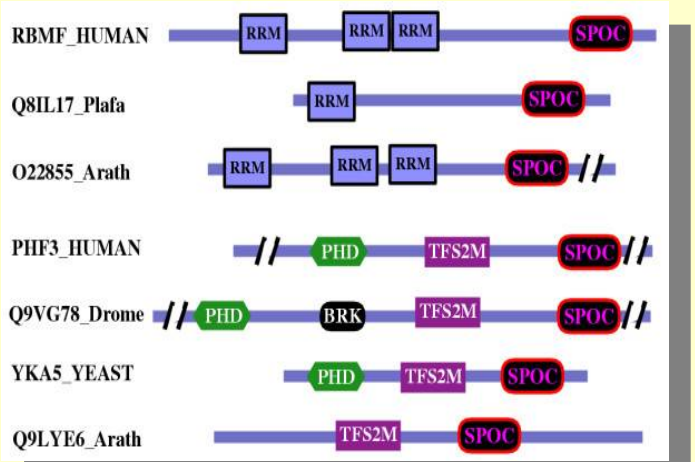


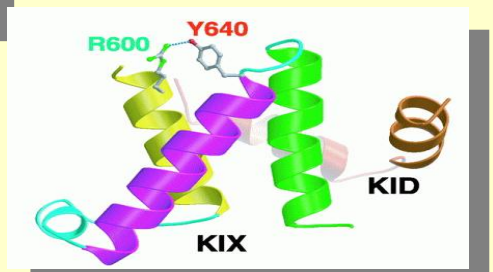


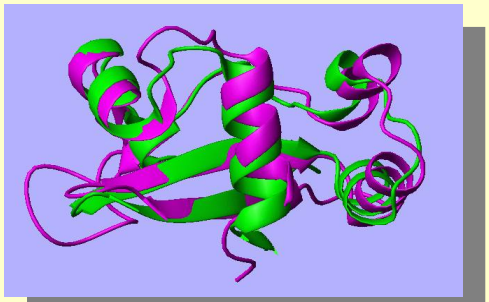








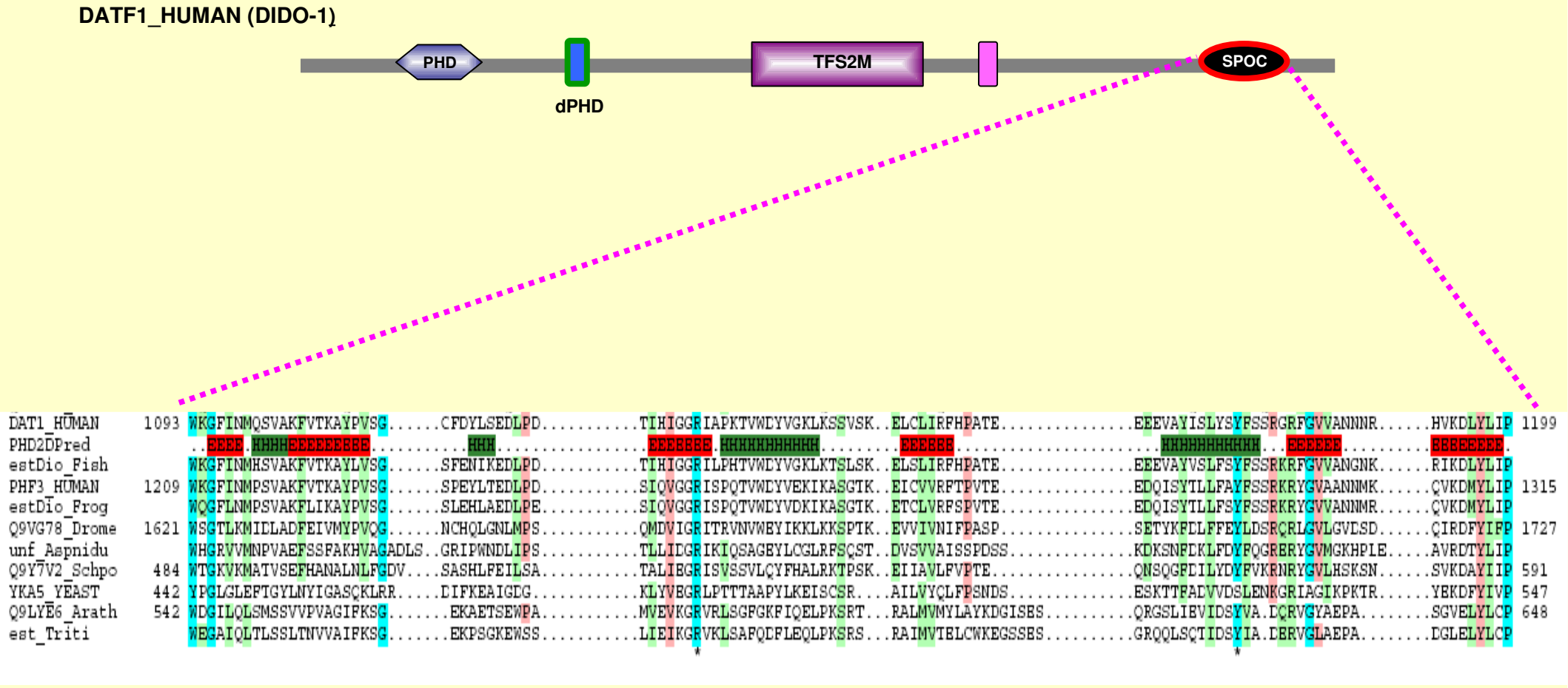


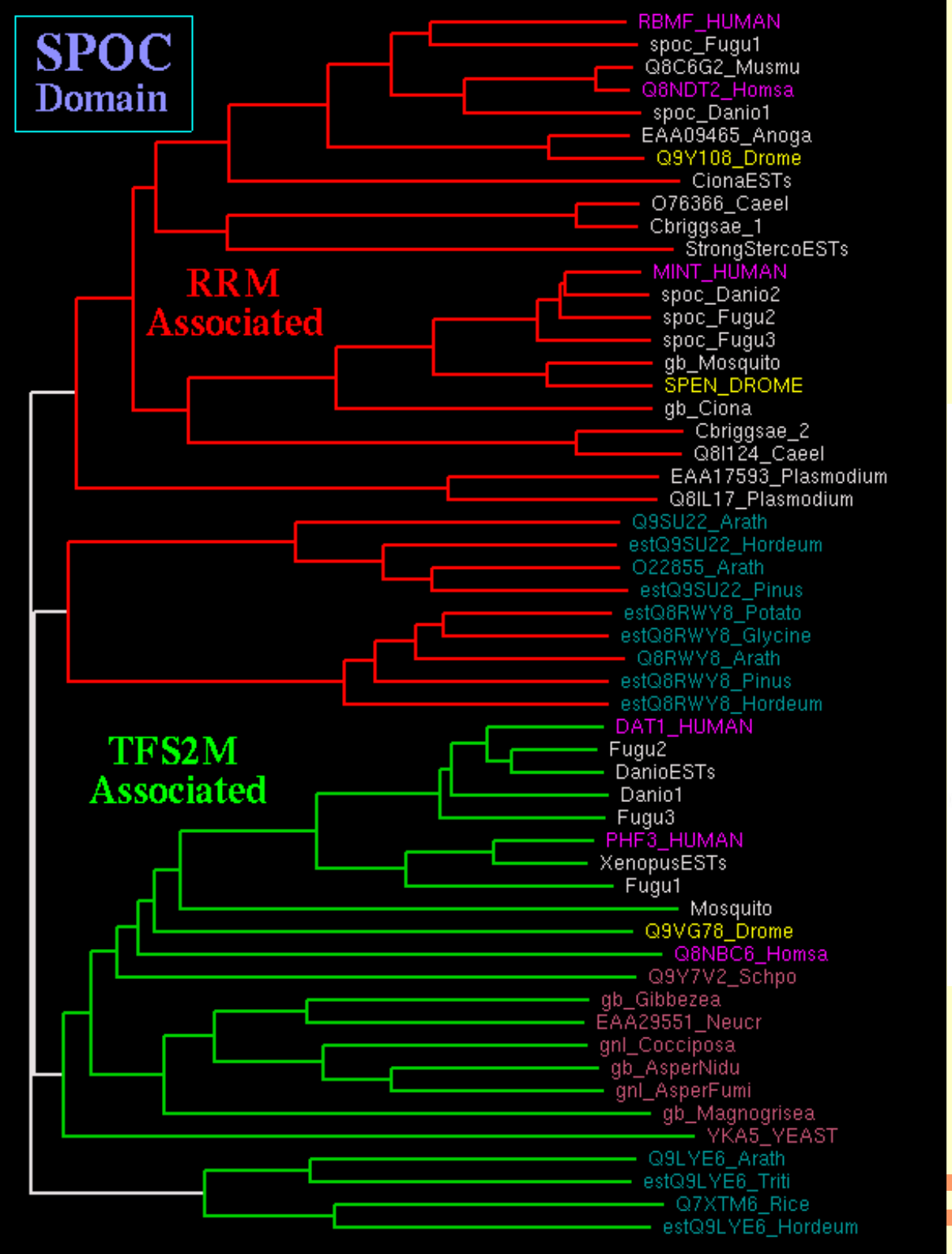


SPOC: A widely distributed domain associated with cancer, apoptosis and transcription.

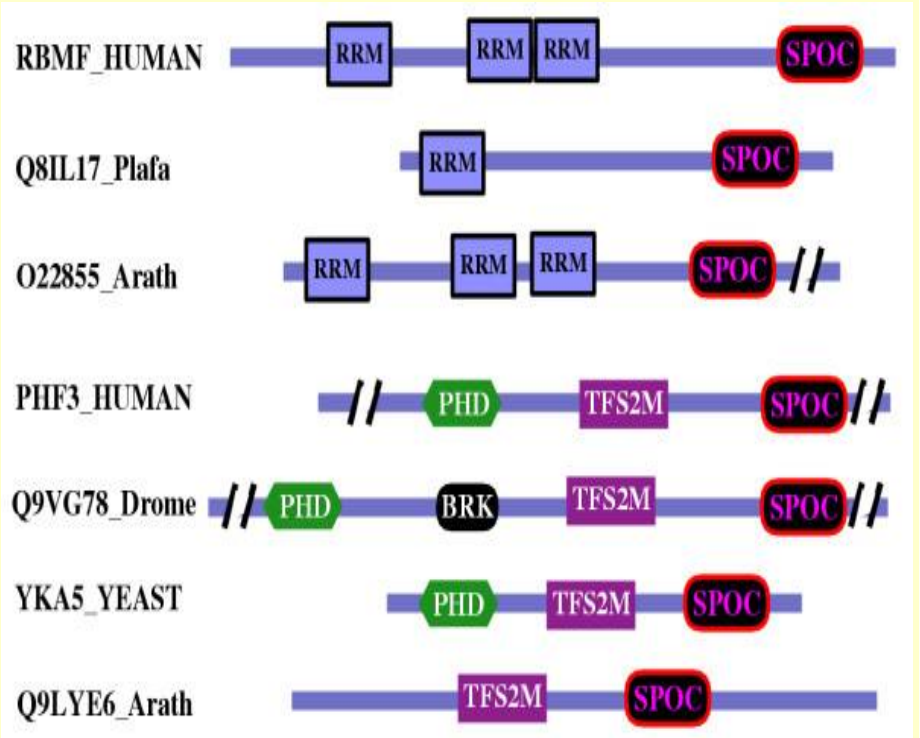
Sanchez-Pulido L, Rojas AM, Van Wely K, Martinez-A C, Valencia A.

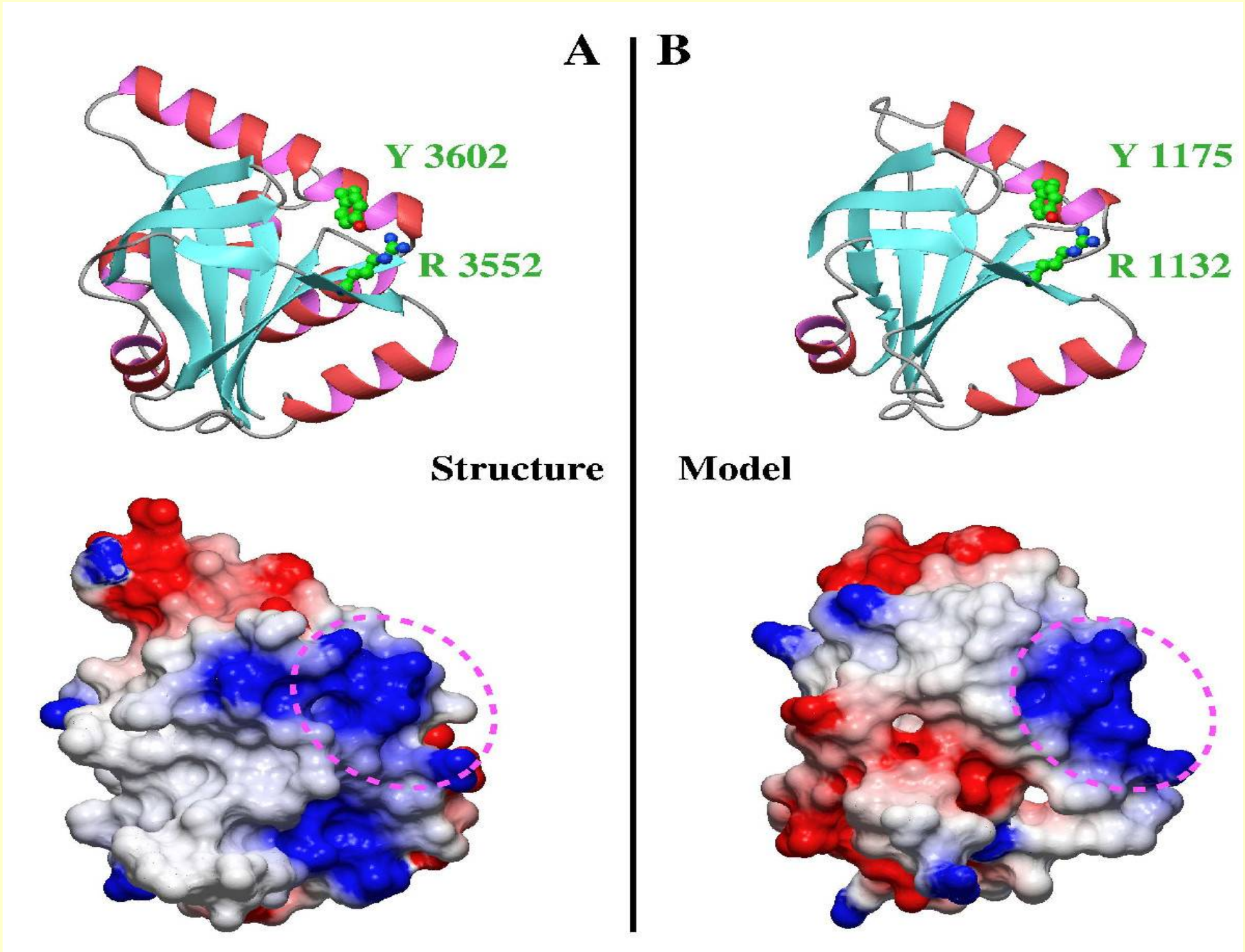
CNB-CSIC





Domain located in, at least, Two Architectures




A
B
Y 3602
R 3552
Y 1175
R 1132
Structure
Model

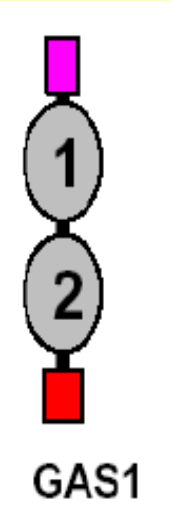
Gas1 is related to the GFRα family and regulates Ret signaling

Cabrera J.R., Sánchez-Pulido L., Rojas A.M., Valencia A.,
Mañes S., Naranjo J.R. & Mellstrom B. (2005)

CNB – CSIC

PROTEÍNA INICIAL: GAS1 (Growth Arrest Specific 1)

FUNCIÓN: Regulación de procesos apoptóticos.

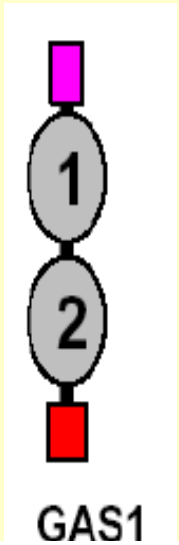


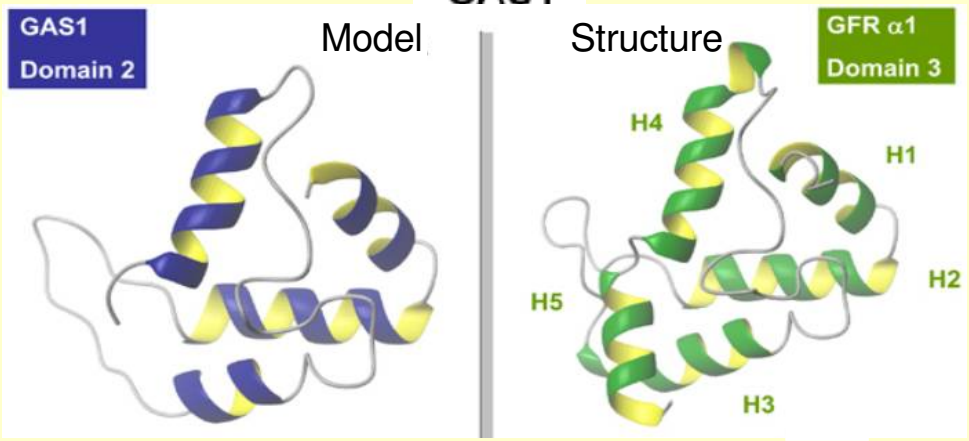
En un primer abordaje:

- Péptido señal
- Duplicación Interna
- GPI-Anclaje

GAS1

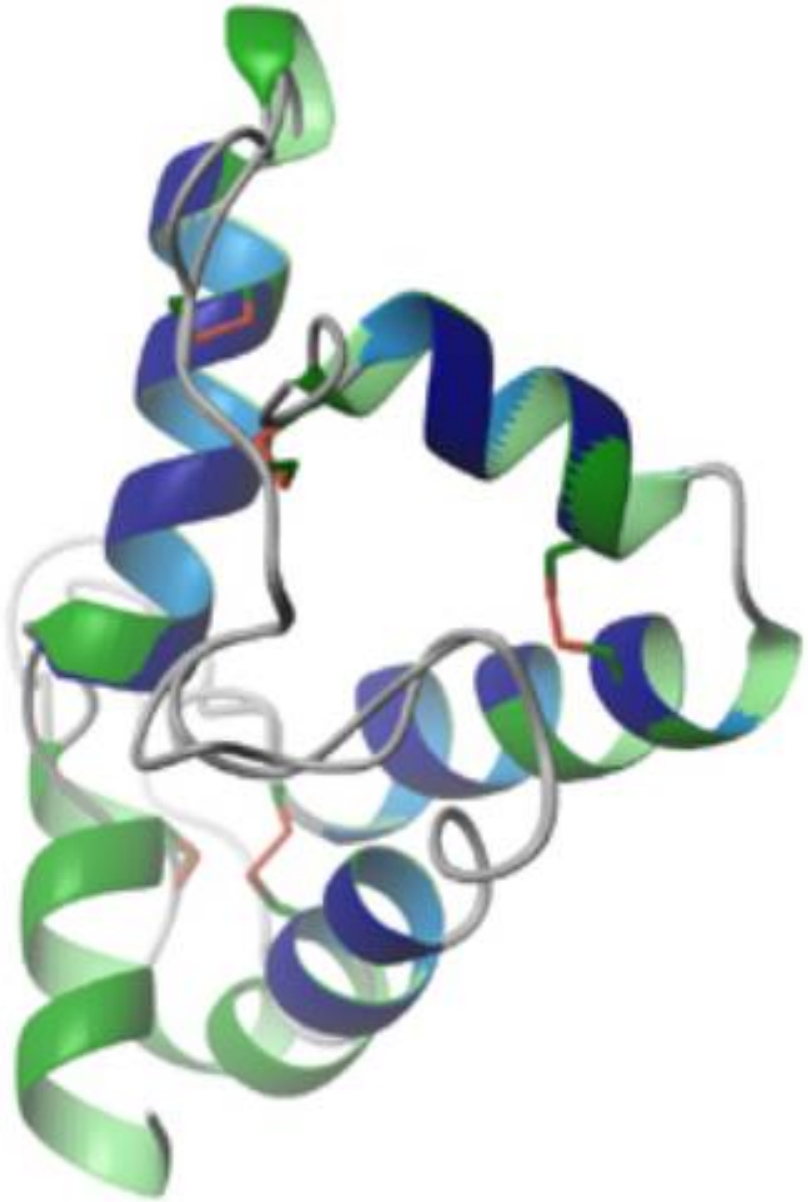
```
GAS1_HUMAN_1     48 CWQALLQCCGE.PECSYAYNQYAEACAPVLAQHGGGDAPGAAAAAFPASAASFSSRWRCP....SHCISALIQLNHTRRGP..........ALEDCDCA.....CDENCKSTKRAIE..PC 146
GAS1_HUMAN_2    166 CTEARRRCDRD.SRCNLALSRYLTYCGKV.....................FNGLRCT....DECRTVIEDMLAMPKVA..........LLNDCVCD...GLERPICESVKENMAR.LC 243
GAS1_MOUSE_1     47 CWQALLQCCGE.PDCSYAYSQYAEACAPVLAQRGGADAPG..PAGAFPASAASSPRWRCP....SHCISALIQLNHTRRGP..........ALEDCDCA.....CDEHCRSTKRAIE..PC 143
GAS1_MOUSE_2    162 CTEARRRCDRD.SRCNLALSRYLAYCGKL.....................FNGLRCT....DECRAVIEDMLAVPKAA..........LLNDCVCD...GLERPICESVKENMAR.LC 239
estGas1_Frog_1   25 CWQAMMRCQEE.AECSYAYRQYVDACSSVLPRPGGEA.....ASSSSSSSSSSRRRCP....SHCISALIQLNHTRWGP..........ALEDCDCA.....MDETCRATKRAIE..PC 116
estGas1_Frog_2  138 CMEARRICEGD.WRCGMSLSRYLTKCGRL.....................FDGLRCT....DECKEVIEDMMRVPKAM..........LLSECECD...GHERPICESIKENMAR.LC 215
Gas1_Fish_1      31 CWKAILKCHGD.PDCHYAYDQYLYACASVI....................SGEHQKCP....SHCISSLIQLNRTQSGP..........ALEDCDCA.....LDPVCRSAKQAIE..PC 107
Gas1_Fish_2     116 CTEARLECEAD.PSCSSAMKDYLFHCRKL.....................FGGERCT....EECRRVIADMRSIPKAQ..........QLDTCVCD...GAERNICEYIKASMKT.FC 193
```

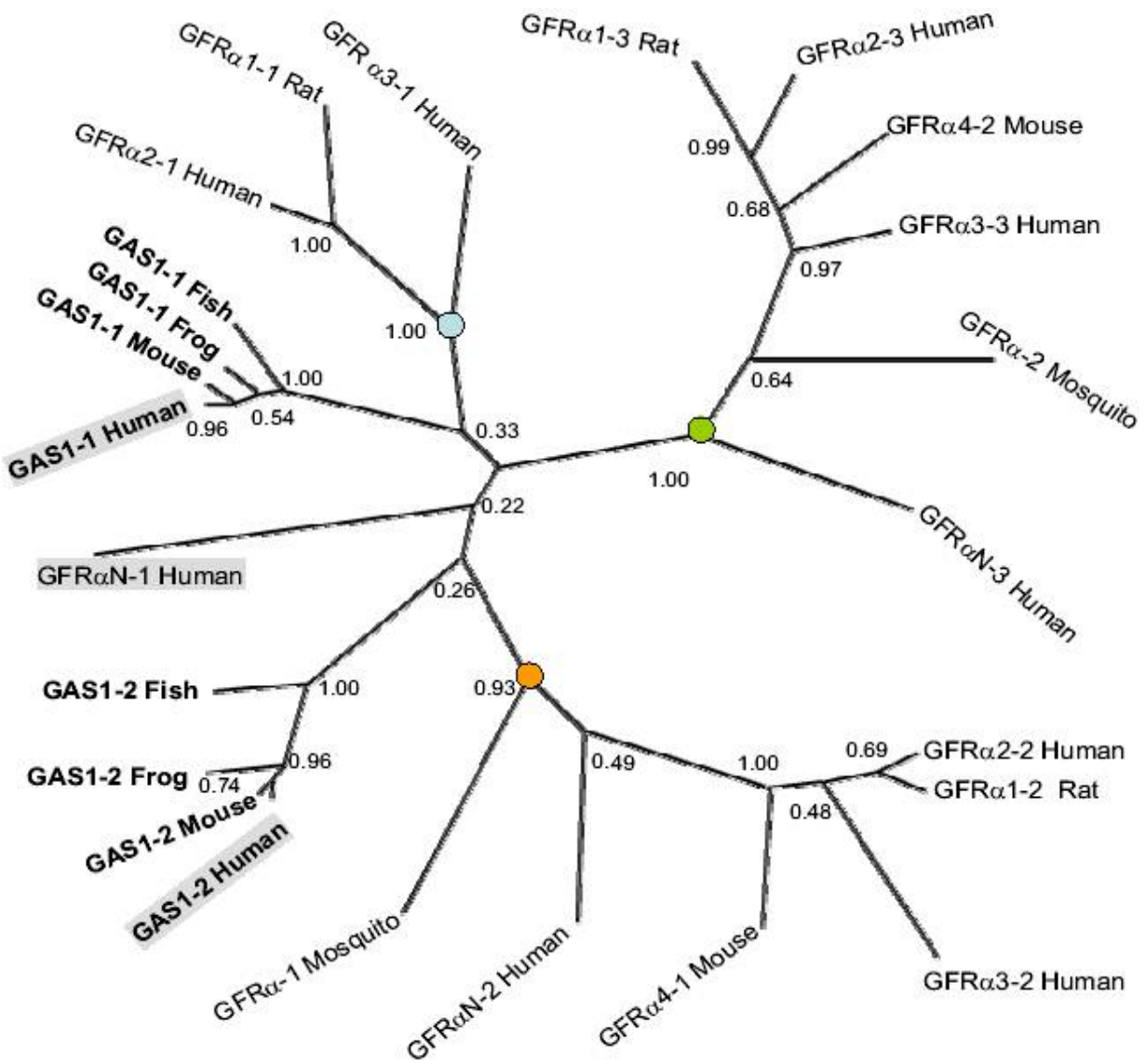




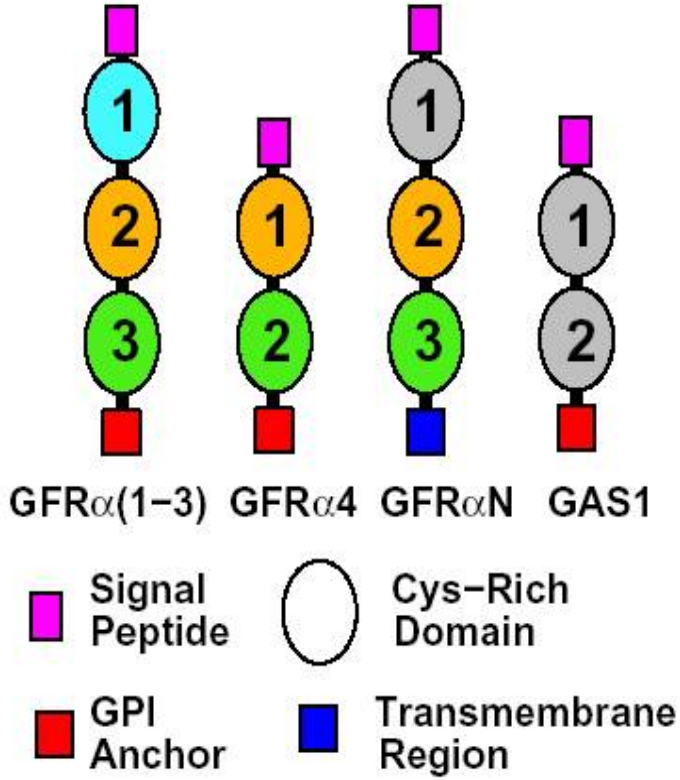
GAS1
Domain 2

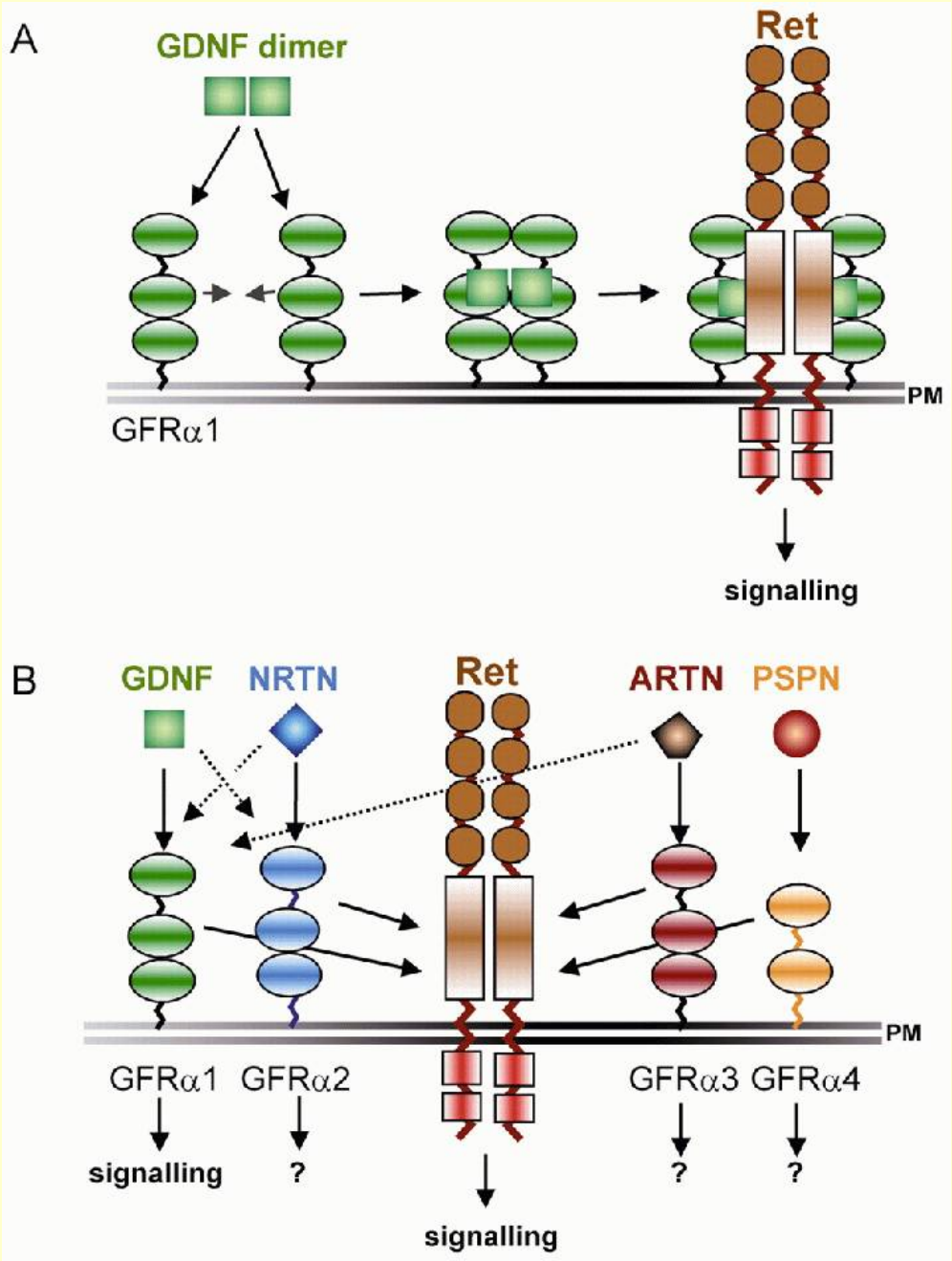
GFR α1
Domain 3





- Arquitectura similar





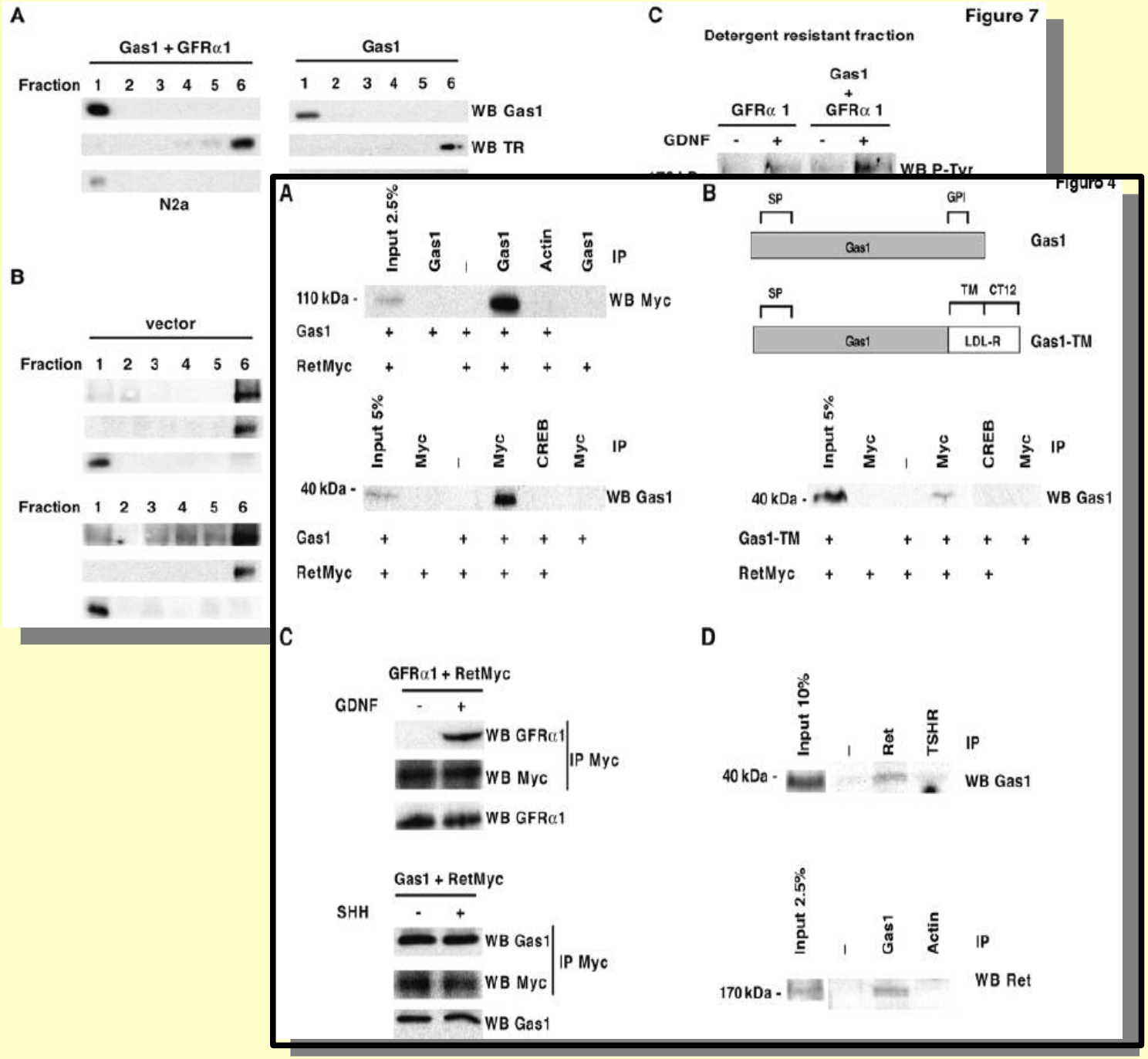
JR Cabrera
CNB-CSIC

BIBLIOGRAFÍA

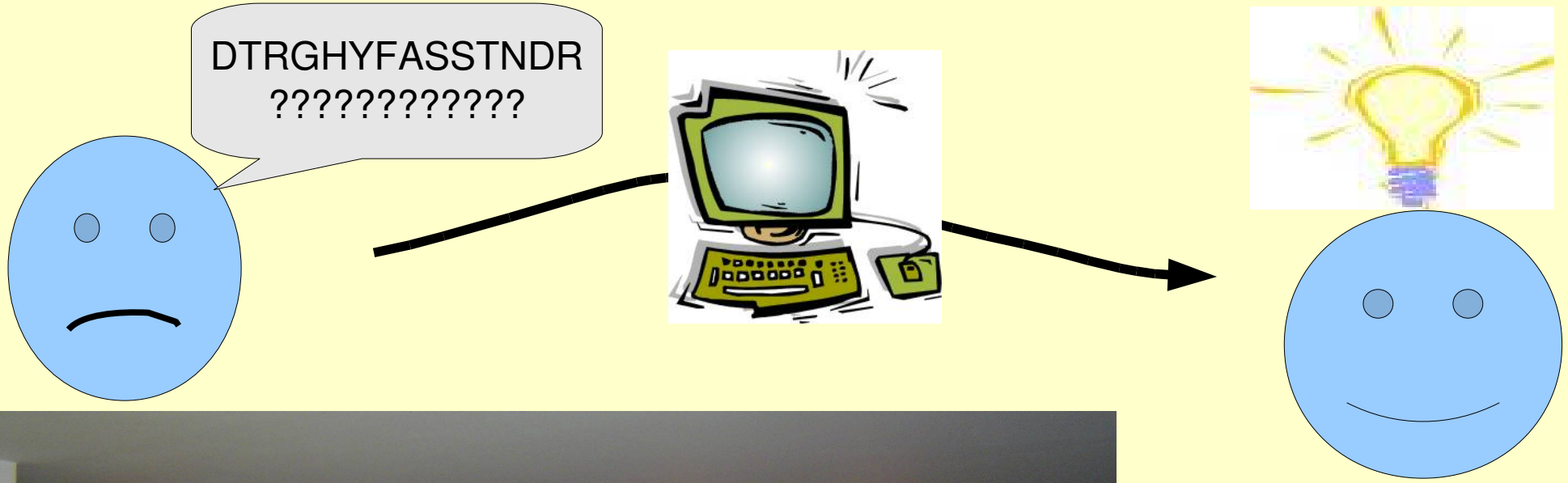
Diferentes factores tróficos o ligandos:

- GDNF Glial cell Derived Neurotrophic Factor
- NRTN Neurturin
- ARTN Artemin
- PSPN Persephin

La Familia **GFRα converge**
en la transducción de la señal
en su **interacción** con
la quinasa Ret -----> ¿Y GAS1...?



Computational predictions supported by experimental analysis.



Jorge Ruben,

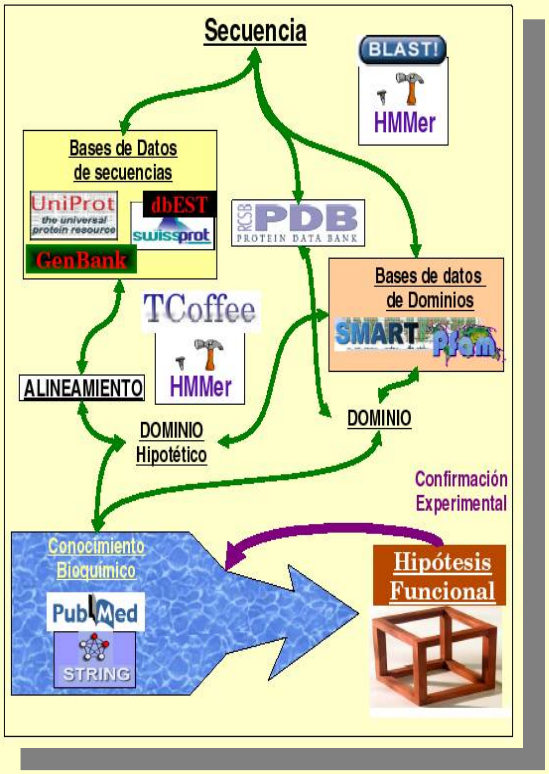
Santos

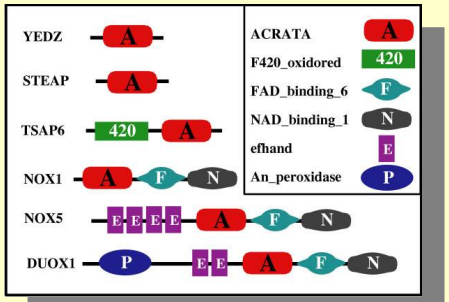
&

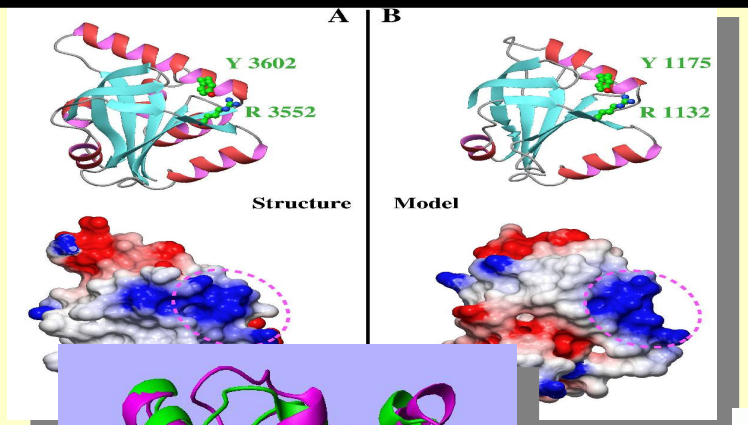
Ana

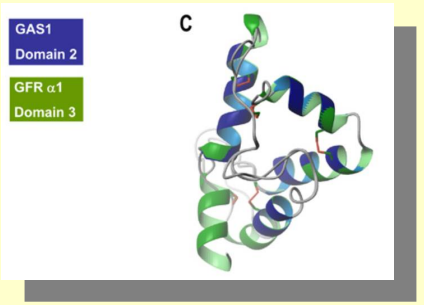
CONCLUSIONE

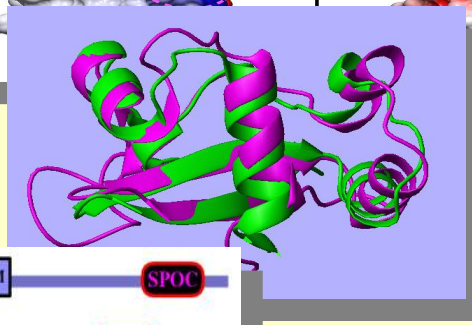
¡Ogni Proteina `e un Mondo!

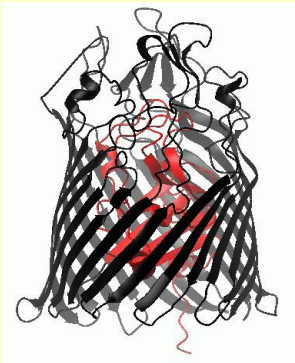


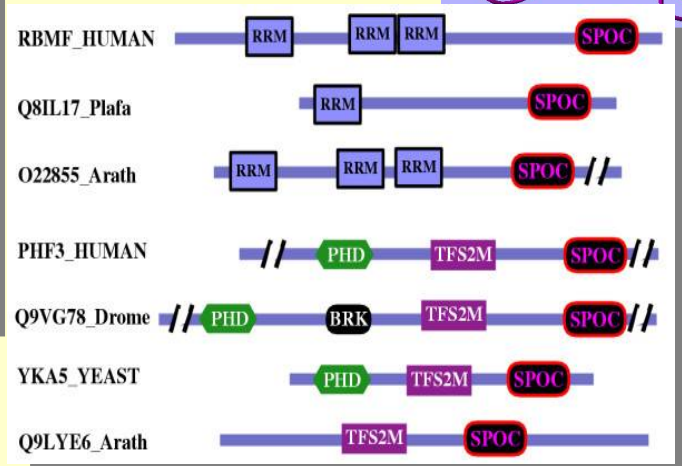


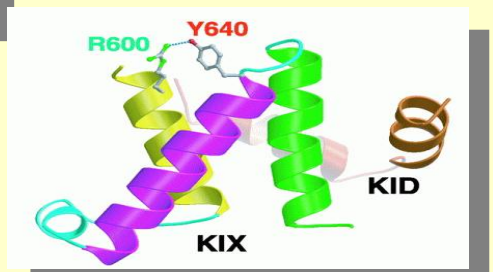












"As a general guide to functional annotation, it should be kept in mind that current methods for genome analysis, even the most powerful and sophisticated of them, facilitate, but do not supplant the work of a human expert."

Eugene Koonin.

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