



#### Bioinformatics for Human Proteomics: Current State and Future Status

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**Tokyo, October 11, 2010** 





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4th SIENA MEETING

FROM GENOME TO PROTEOME: KNOWLEDGE ACQUISITION AND REPRESENTATION

Vature Precedings : doi:10.1038/npre.2010.5050.1 : Posted 20 Oct 2010

Sept. 4-7, 2000, Siena, Italy

Review

TRENDS in Biotechnology Vol.19 No.5 May 2001

#### The human proteomics initiative (HPI)



8<sup>th</sup> SIENA MEETING

FROM GENOME TO PROTEOME:

INTEGRATION AND PROTEOME COMPLETION

Siena, Italy, August 31st- September 4th, 2008 Auditorium Giurisprudenza e Scienze Politiche



UniProt Releases 'Complete' Set of 20K Human Proteins at Siena Meeting

[September 4, 2008]

Exactly 10 years ago, at the 4th Siena meeting, we proposed to annotate in Swiss-Prot all the human proteins

### A 'complete' set of annotated human proteins

- In September 2008, we had annotated **20'330** human protein entries in UniProtKB/Swiss-Prot;
- They originate from about **20'400** protein-coding genes;
- Why 'about'?
  - There are sets of genes that encode for identical proteins (example: 14 genes code for histone H4);
- There are genes that codes for two or more proteins that have nothing in common in term of their sequence (bicistronic or alternative splicing);
- There are some other weird cases!
- The precise definition of what is a gene is dependent on who is using/making that definition.

### Since...

- Since the beginning of 2009, we have added 130 «new» sequences, but we have «deleted» 171 proteins;
- Our gut feeling is that we are slowly but inexorably creeping toward slightly under 20'000 human-protein coding genes.

# Alternative isoforms

- Produced by alternative splicing, promoter usage or initiation;
   Currently we have 14'700 additional isoforms in about 7'600 entries;
  - This means that **38%** of the protein-coding genes are already annotated to code for at least 2 different protein sequences;
  - We estimate (based on an in-depth analysis of genes encoded on chromosome 13) that this number will rise above **60**% and the average number of isoforms to 3;
  - This mean that we can already estimate that there is probably about **50'000** different human proteins that are produced by as many (or even more) transcripts.



# Sequence variants

We have information concerning about **63'000** SAP (single amino-acid polymorphisms);

- **20'000** are linked to diseases. This information is mined from the literature and from disease-specific databases;
- This means that, excluding disease variants, there is already an average of 2 SAPs per protein;
- The 'non-disease' variants are obtained from a variety of sources (HAPMAP, NIEHS-SNPs, etc);
- They will increasingly come from whole human genome sequencing efforts (1'000 genomes, etc).

# Caveat about variants

The canonical human genome sequence is artefactual. There is no such thing as an average genome;

Some reported variants represent in fact the «majority» sequence;

In humans, variability at level of proteins is not restricted to SAPs, one needs also to take into account:

- Segregating pseudogenes (example: olfactory receptors);
- Copy number variation;
- Active retrotransposable elements (LINE-1, ERVs);
- The solution:to gradually move to what microbiologists have already embraced: a pangenome.

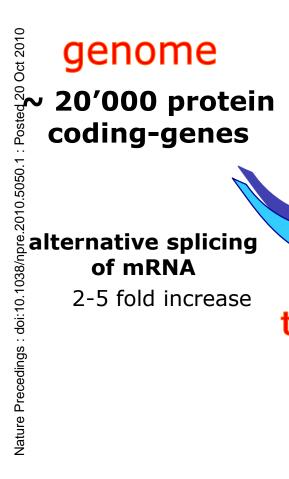
### **Post-translational modifications**

- We have about 80'000 annotated PTMs;
- Only half of them have been experimentally obtained;
- The rest are predicted or inferred from experiments done in other species;
- We are just looking at the tip of the iceberg. But proteomics studies are starting to address this issue seriously;
  - If we make a very modest estimate of 5 different PTMs per protein and that they may be independently regulated, you already get a **100x** increase in the number of protein species in our body (to a total of **5 million**).

#### The PTM world is still largely uncharted (3R)-3-hydroxyasparagine, (3R)-3-hydroxyasparate, (3S)-3-hydroxyasparagine, 1'-histidyl-3'-tyrosine, 1-

thioglycine, 2',4',5'-topaquinone, 2,3-didehydroalanine, 3'-(S-cysteinyl)-tyrosine, 3-hydroxyproline, 3oxoalanine, 4-amino-3-isothiazolidinone serine, 4-carboxyglutamate, 4-hydroxyproline, 5-glutamyl, 5glutamyl glycerylphosphorylethanolamine, 5-hydroxylysine, 5-imidazolinone, ADP-ribosylasparagine, ADP-ribosylcysteine, ADP-ribosylserine, Allysine, Arginine amide, Asparagine amide, Aspartate 1-(Ehondroitin 4-sulfate)-ester, Asymmetric dimethylarginine, Beta-decarboxylated aspartate, Cholesterol glycine ester, Citrulline, Cysteine methyl ester, Cysteine sulfenic acid, Cysteinyl-selenocysteine, Reamidated asparagine, Deamidated glutamine, Dimethylated arginine, Diphthamide, Disulfide bond, ©PI-anchor amidated alanine, GPI-anchor amidated asparagine, GPI-anchor amidated aspartate, GPIanchor amidated cysteine, GPI-anchor amidated glycine, GPI-anchor amidated serine, Glutamic acid 1amide, Glutamine amide, Glycine amide, Glycyl adenylate, Glycyl lysine isopeptide, Hydroxyproline, Hydroxyproline, Hypusine, Isoglutamyl cysteine thioester, Isoglutamyl lysine isopeptide, Isoleucine amide, Leucine amide, Leucine methyl ester, Lysine amide, Lysine tyrosylquinone, Methionine amide, N,N,Ntimethylalanine, N-acetylalanine, N-acetylaspartate, N-acetylcysteine, N-acetylglutamate, Nacetylglycine, N-acetylmethionine, N-acetylproline, N-acetylserine, N-acetylthreonine, N-acetylvaline, Nmyristoyl glycine, N-palmitoyl cysteine, N-palmitoyl glycine, N-pyruvate 2-iminyl-valine, N4,N4dimethylasparagine, N6,N6,N6-trimethyllysine, N6,N6-dimethyllysine, N6-(pyridoxal phosphate)lysine, N6-(retinylidene)lysine, N6-1-carboxyethyl lysine, N6-acetyllysine, N6-biotinyllysine, N6-carboxylysine, N6-Ipoyllysine, N6-methylated lysine, N6-methyllysine, N6-myristoyl lysine, Nitrated tyrosine, O-(pantetheine) 4 - phosphoryl)serine, O-AMP-threonine, O-AMP-tyrosine, O-acetylserine, O-acetylthreonine, O-decanoyl serine, O-palmitoyl serine, Omega-N-methylarginine, Omega-N-methylated arginine, Omega-Rydroxyceramide glutamate ester, Phenylalanine amide, Phosphatidylethanolamine amidated glycine, Phosphohistidine, Phosphoserine, Phosphothreonine, Phosphotyrosine, PolyADP-ribosyl glutamic acid, Proline amide, Pyrrolidone carboxylic acid, Pyruvic acid, S-(dipyrrolylmethanemethyl)cysteine, S-8alpha-FAD cysteine, S-Lysyl-methionine sulfilimine, S-cysteinyl cysteine, S-farnesyl cysteine, S-geranylgeranyl cysteine, S-glutathionyl cysteine, S-methylcysteine, S-nitrosocysteine, S-palmitoyl cysteine, S-stearoyl cysteine, Sulfoserine, Sulfotyrosine, Symmetric dimethylarginine, Tele-8alpha-FAD histidine, Telemethylhistidine Thyroxine Trijodothyronine Tyrosine amide Valine amide

#### From genome to proteome



proteome

~ 5'000'000 different proteins

post-translational modifications of proteins (PTMs) 50-100 fold increase

#### transcriptome

~ 50 to 100'000 transcripts (mRNAs)

# **Protein complexity**

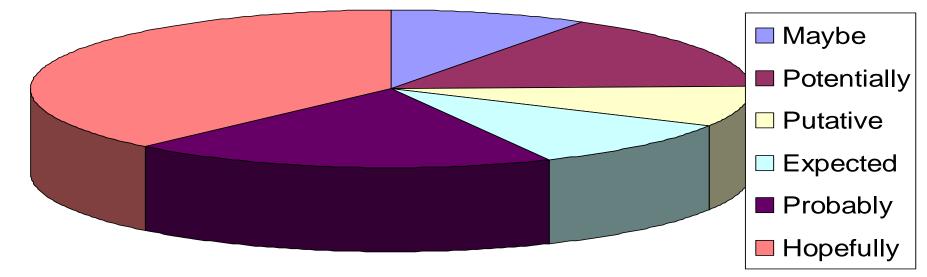
# Breakdown in term of Protein Evidence (PE) of human proteins

- 1: Evidence at protein level 13340 (65.8%)
- 2: Evidence at transcript level 6018 (29.7%)
- 3: Inferred from homology
- 4: Predicted
- 5: Uncertain

- 210 ( 1.0%) 97 ( 0.5%) 600 ( 2.9%)
  - 600 ( 2.9%)

But even for the 66% where there is evidence, at protein level, of the protein existence, there is still a lots to be done at the proteomic level (PTMs, interactions, subcellular location, tissue-specificity, etc). In the framework of the annotation effort to produce a complete set of human entries, we were confronted by how little is known on the function of many human proteins....

#### **Characterization status of human proteins**



# CAL PHO

#### Computer Analysis and Laboratory Investigation of Proteins of Human Origin

A new group of the University of Geneva and the Swiss Institute of Bioinformatics

Directed by Amos Bairoch and Lydie Lane







# The 3 missions of CALIPHO

- Carry out laboratory experiments on selected sets of uncharacterized human proteins to discover their function;
- Develop neXtProt, an ambitious new knowledge resource centered around human proteins;
- Organize a collective effort that pools resources around the world with the goal of functionally characterize all human proteins.



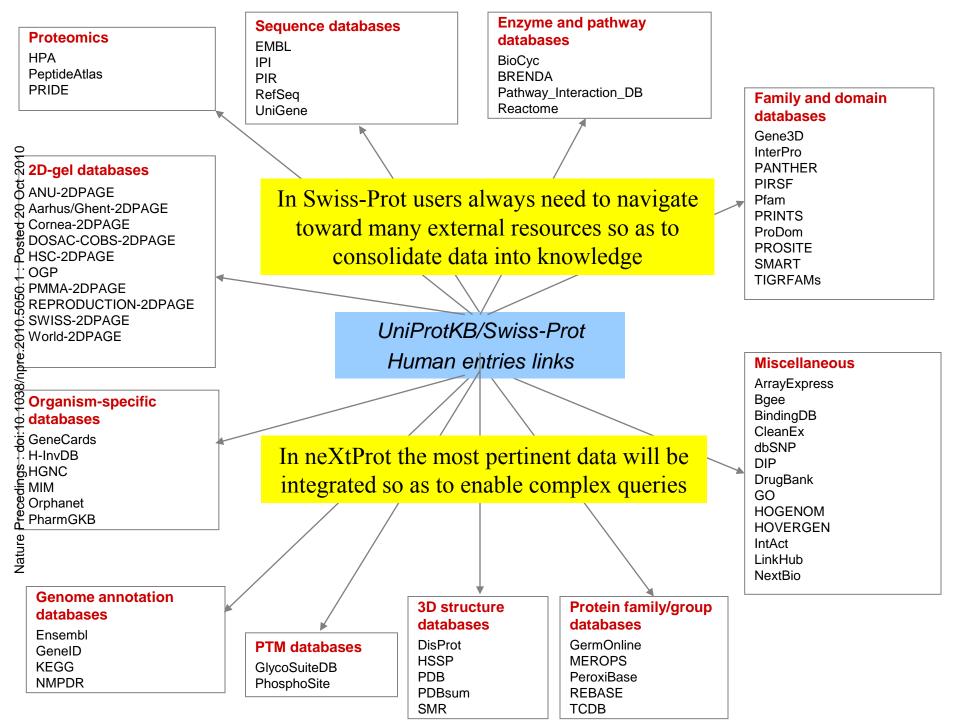
**What**: a comprehensive resource that complements SIB/EBI Swiss-Prot human protein annotation efforts. neXtProt is expected to become the central resource of human protein-centric information;

How:

 by mining, in the most appropriate way and with our stringent quality criteria, many external data resources.

In this context we plan to add additional protein/protein and protein/small molecules interactions, **proteomics data**, pathway information, tissular and cellular expression from antibodies, variation data (such as SNP frequencies), siRNA screen data, microRNA targets, microarray expression data, phylogenetic profiling, etc;

 by integrating experimental results from an extensive network of collaborating laboratories.



# What is not neXtProt?

- neXtProt is not Swiss-Prot "Plus";
- Yes, neXtProt will contains a wealth of data not available in Swiss-Prot;
- But the real challenge is to build a real knowledge platform where our users can ask meaningful questions and hopefully obtain the answers that they seek!



# When and what

- We will have a first public version out in October 2010
  - In terms of data, it will contains:
    - All of Swiss-Prot human data: sequences and annotations;
    - Human Proteome Atlas organ and tissue expression information from antibodies;
    - Metadata on mRNA expression from microarrays and ESTs from Bgee (analyzed from ArrayExpress and UniGene);
    - Additional SNPs from dbSNP and Ensembl;
    - Chromosomal location and exons mapping from Ensembl;
    - Affymetrix and Illumina chip sets identifiers.
  - In terms of interface, it will offers:
  - An intuitive query interface;
  - Different specialized views (function, medical, expression, etc.);
  - The possibility to tag and label proteins.

		Home Recent activites 👻 🛧 Favorites 👻 📼 My labels 👻									
neXtprot	ETA	domain v pdz publications v borg	🛱 Go								
2010		Did you mean: org	clear search								
Result filter	_										
Disease		Categories: All   Proteins (10)   Publications (0) export -   Show 10	✓ summary   details								
Goo term		Proteins : 10 results									
UniProt keyword		$\sim$ No(1)/H(1) exchange regulatory cofector NHE DE1 (SLC042D4) [NX_014745]									
Subcellular location	1	☆ Na(+)/H(+) exchange regulatory cofactor NHE-RF1 (SLC9A3R1) [NX_014745]									
∽ Post-translational m	nodif.	. ☆ Protein LAP2 (ERBB2IP) [NX_Q96RT1]									
Nacetylserine	1	☆ Protein scribble homolog (SCRIB) [NX_Q14160]									
Fallosphotyrosine	5										
Bosphothreonine	6	Tight junction protein ZO-2 ( <i>TJP2</i> ) [NX_Q9UDY2]									
Resphoserine Tresue	9	Na(+)/H(+) exchange regulatory cofactor NHE-RF2 (SLC9A3R2) [NX_Q15599]									
۲Tissue ی		☆ LIM domain only protein 7 (LMO7) [NX_Q8WWI1]									
cedinç		Amyloid beta A4 precursor protein-binding family A member 1 (APBA1) [NX_Q02410]									
Nature Precedings		☆ Afadin ( <i>MLLT4</i> ) [NX_P55196]									
Natu		☆ Sorting nexin-27 (SNX27) [NX_Q96L92]									
		Amyloid beta A4 precursor protein-binding family A member 2 (APBA2) [NX_Q99767]									



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Family name/EC number	Categories: All   Proteins (204)   Publications (490) export V   Show 10 V summary   details							
Disease	Proteins : 10 of 204 results							
Usher syndrome ty 2								
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Ectodermal dyspla 1	E-Cad/CTF2 promotes non-amyloidogenic degradation of Abeta precursors. Has a strong inhibitory effect on APP C99 and C83 production.Cadherins are calcium-dependent cell adhesion proteins. [more]							
	Gene location: 16q22.1 Isoforms: 1 Variants: 35 PTMs: 6							
Deafness autosoma1 Hypotrichosis and 1	3D structure: yes Proteomics: no Tissue expression: yes Mutagenesis: yes							
Hypotrichosis con 1 Epidermolysis bul 1	Cadherin-3 (CDH3) [NX_P22223]							
Epidermolysis bul 1	Cadherins are calcium dependent cell adhesion proteins. They preferentially interact with themselves in a homophilic manner in connecting cells; cadherins may thus contribute to the sorting of heterogeneous cell types.							
Palmoplantar kera 1	Gene location: 16q22.1 Isoforms: 2 Variants: 15 PTMs: 3							
Deafness autosoma1 Skin fragility-wo 1 Usher syndrome ty 1	3D structure: no Proteomics: no Tissue expression: yes Mutagenesis: no							
Skin fragility-wo 1	☆ Cadherin-13 (CDH13) [NX_P55290]							
Usher syndrome ty 1	Cadherins are calcium dependent cell adhesion proteins. They preferentially interact with themselves in a homophilic manner in							
Limb-girdle muscu 1	connecting cells; cadherins may thus contribute to the sorting of heterogeneous cell types. May act as a negative regulator of							
GO term	neural cell growth.							
JniProt keyword	Gene location: 16q23.3 Isoforms: 1 Variants: 2 PTMs: 9 3D structure: yes Proteomics: no Tissue expression: yes Mutagenesis: no							
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Subcellular location	☆ Cadherin-23 (CDH23) [NX_Q9H251]							
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lissue	connecting cells. [more]							
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	☆ Cadherin-5 (CDH5) [NX_P33151]							

Cadherins are calcium dependent cell adhesion proteins. They preferentially interact with themselves in a homophilic manner in connecting cells; cadherins may thus contribute to the sorting of heterogeneous cell types. [more] Gene location: 16q21 Isoforms: 1 Variants: 5 PTMs: 8 3D structure: no Proteomics: no Tissue expression: yes Mutagenesis: no

# A variety of views

teins	CDH1 » Cadh	erin-1	☆ star 📼 Label			
teins Inction dical ression	E-Cad/CTF1 ; E-C Gene name: CDH	n as: Epithelial cadherin (E-cadherin); CD antigen CD324 . Cleaved into: ad/CTF2 ; E-Cad/CTF3 . 1 . been shown to exist at protein level	✓ extend overview 1 58 1 GENE REF ISO			
ractions alisation						
ansauon	Function					
uence annotations	<ul> <li>show evidences</li> </ul>					
uence annotations ictures ntifiers ne ns ntifiers	OVERVIEW	Cadherins are calcium-dependent cell adhesion proteins. They preferentially homophilic manner in connecting cells; cadherins may thus contribute to the types. CDH1 is involved in mechanisms regulating cell-cell adhesions, mobility cells. Has a potent invasive suppressor role. It is a ligand for integrin alpha-E	sorting of heterogeneous cell y and proliferation of epithelial	Curated UniProtKB		
tifiers		E-Cad/CTF2 promotes non-amyloidogenic degradation of Abeta precursors. on APP C99 and C83 production.	Has a strong inhibitory effect	Curated UniProtKB		
erences lications ents missions o resources	GO FUNCTIONAL ANNOTATION	Molecular Functions           RPTP-like protein binding         definition         [GO:0042153]	1 re	EA ENSEMBL		
o resources		Beta-catenin binding definition [GO:0008013]	1	IPI UniProtKB		
		Calcium ion binding definition [GO:0005509]	1 re	EA ENSEMBL		
		Cell adhesion molecule binding definition [GO:0050839]	1	NAS BHF-UCL		

#### VAV1 » Proto-oncogene vav

☆ star 💁 Label

Gene name: VAV1.	<pre>vextend overview 1 25 1</pre>
Bis protein have been shown to exist at protein level	

#### Resitional Annotations referenced on Iso 1



#### Isoform Iso 1 845 aa, Mass: 98314 Da, pl: 6.2

Actions: FASTA , Blast: full sequence on selection

241	EDLLRVHTHF	LKEMKEALGT	PGAANLYQVF	IKYKERFLVY
281	GRYCSQVESA	SKHLDRVAAA	REDVQMKLEE	CSQRANNGRF
321	TLRDLLMVPM	QRVLKYHLLL	QELVKHTQEA	MEKENLRLAL
361	DAMRDLAQCV	NEVKRDNETL	ROITNFOLSI	ENLDQSLAHY
401	GRPKIDGELK	ITSVERRSKM	DRYAFLLDKA	LLICKRRGDS
441	YDLKDFVNLH	SFQVRDDSSG	DRDNKKWSHM	FLLIEDQGAQ
481	GYELFFKTRE	LKKKWMEQFE	MAISNIYPEN	ATANGHDFOM
521	FSFEETTSCK	ACQMLLRGTF	YQGYRCHRCR	ASAHKECLGR
561	VPPCGRHGQD	FPGTMKKDKL	HRRAQDKKRN	ELGLPKMEVF
601	QEYYGLPPPP	GAIGPFLRLN	PGDIVELTKA	EAEQNWWEGR
641	NTSTNEIGWF	PCNRVKPYVH	GPPQDLSVHL	WYAGPMERAG
681	AESILANRSD	GTFLVRQRVK	DAAEFAISIK	<b>NANAEAKHIKI</b>
721	MTAEGLYRIT	EKKAFRGLTE	LVEFYQQNSL	KDCFKSLDTT
761	LQFPFKEPEK	RTISRPAVGS	TKYFGTAKAR	YDFCARDRSE
801	LSLKEGDIIK	ILNKKGQQGW	WRGEIYGRVG	WFPANYVEED
841	YSEYC			

SD Castegory eC eC eC eC eC eC eC eC eC eC eC eC eC	Names	Positions	Length	Description	Evidences	Also present in isoforms
Prec	Domain	402 - 504	103	PH	1	
	Zinc finger	515 - 564	50	Phorbol-ester/DAG-type	1	
Nature	Domain	617 - 660	44	SH3 1	1	
2	Domain	671 - 765	95	SH2	1	
	Domain	782 - 842	61	SH3 2	1	
PROCESSING	Mature protein	1 - 845	845	Proto-oncogene vav	1	

#### **Biophysicochemical properties**

Kinetic para	ameters
K <sub>M</sub>	663.5 uM for D-methylphenidate
K <sub>M</sub>	43 mM for ethanol
K <sub>M</sub>	116 uM for cocaine
K <sub>M</sub>	775.7 uM for L-methylphenidate
K <sub>M</sub>	106.6 uM for p-nitrophenyl acetate
V <sub>max</sub>	493.9 nmol/min/mg enzyme with p-nitrophenyl acetate as substrate
V <sub>max</sub>	177.2 pmol/min/mg enzyme with D-methylphenidate as substrate
V <sub>max</sub>	1701.1 pmol/min/mg enzyme with L-methylphenidate as substrate
Dependenc	e
рН	Optimum pH is 6.5.
	Tissue expression



# The future

- Our vision is to gradually build up neXtProt, not only by adding new data resources but:
  - By integrating state of the art data mining tools;
  - By integrating some forms of "social networking" functionalities allowing researches to share ideas and data;
  - By enabling the modeling of hypothesis inside the framework of the platform.
- To work closely with HUPO HPP stakeholders to define what proteomicsderived data we will represent in neXtProt.

#### A prototype of a future proteomics view

n		FNDC3A » Fibronectin type-III domain-containing protein 3A					☆ favorizelabel		
di i	Protein also know Gene name: FN	na stanon en en en en esta esta esta esta esta esta esta esta	expressed in odontoblas	<b>*</b> e)	tend overview	1 15 2			
sion	Family name: FN								
tions ation	One or more isof	forms of this protein h	ave been shown to exis						
mics	Positional Ann	otations reference	d on Iso 1	Isoform Iso 1 1198 aa, Mass: 131852 Da, pl: 6.29					
res	Proteomics	🛛 Topology 🗹 Domai	ns/regions 🗌 Modified r	esidues 🗌 Variants All/None			ull sequence on selection		
ers							TREATED STITITIES INTERIOR VARY VIEW		
	Isoform Iso	1					SPHPPLP GFIPVPTMMP PPPRHMYSPV TGAGDMTTQY DAHSTHG RSNFRDERSS KTYERLQKKL KDRQGTQKDK		
	Mature protein Fib	ronectin type-III domain-co	ontaining protein 3A				PINEHNG LIKGQIAGGI NTGSAKIKSG KGKGGTQVDT		
ers	Antibody	HPA008927		HPA012825			ALLSNIV KPVASDIQAR TVVLTWSPPS SLINGETDES		
es	1 iuw analida						STGKDGK YKSVYVGEET NITLNDLKPA MDYHAKVQAE FTTLSCE PDIPNPPRIA NRTKNSLTLQ WKAPSDNGSK		
	Liver peptide		0 0	U	401 I	ONFVLEWDE GKG	NGEFCQC YMGSQKQFKI TKLSPAMGCK FRLSARNDYG		
tions	SRM peptide		0				SCAPSMP ASPVLTKAGI TWLSLQWSKP SGTPSDEGIS		
1	Composition bias	Composition bias				501 YILEMEEETS GYGFKPKYDG EDLAYTVKNL RRSTKYKFKV IAYNSEGKSN 551 PSEVVEFTTC PDKPGIPVKP SVKGKIHSHS FKITWDPPKD NGGATINKYV			
sions			Instance I Strange In Burnary III				MIYSGAT REHLCDRLNP GCFYRLRVYC ISDGGQSAVS		
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							PPQVTCR SATCAQVNWE VPLSNGTDVT EYRLEWGGVE		
(2)							YEIKGLS PATTYYCRVQ ALSVVGAGPF SEVVACVTPP		
( <b>2</b> )							DDEIENP HYSPSTCLAI SWEKPCDHGS EILAYSIDFG IINNLQP DTTYRIRIQA LNSLGAGPFS HMIKLKTKPL		
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election	Category	Names	Positions Length	Description		Evidences	Also present in isoforms		
	PROTEOMICS	Antibody	142 - 274 133	HPA008927 (HPA 🚱)			2		
		Peptide	224 - 236 13	Liver HUPO Project (PeptideAtlas 🚱)			2		
		Peptide	224 - 236 13	SRM (SRMAtlas 🔄)			2		
		Peptide	261 - 271 11	Liver HUPO Project (PeptideAtlas 🚱)			2		
		Peptide	261 - 271 11	SRM (SRMAtlas 🖗)			2		
		Peptide	518 - 528 11	Liver HUPO Project (PeptideAtlas 🖉)			2		
		Peptide	599 - 610 12	SRM (SRMAtlas 🔄)			2		
		Peptide	628 - 635 <b>8</b>	SRM (SRMAtlas 🚱)			2		
		Antibody	776 - 910 135	HPA012825 (HPA 🚱)			2		
		Peptide	957 - 968 12	SRM (SRMAtlas 🚱)			2		

# You can already start test drive neXtProt in a few days

Just go to beta.nextprot.org and sign up

### CALIPHO@UniGe\_and\_SIB

#### neXtProt content:

- Coordinator: Pascale Gaudet
- Biocurators: Guislaine Argoud-Puy, Isabelle Cusin, Paula Duek

#### neXtProt software developers:

 Olivier Evalet, Alain Gateau, Anne Gleizes, Catherine Zwahlen and Alexandre Masselot (GeneBio)

#### **Bioinformatics research:**

Anais Mottaz, Anne-Lise Veuthey (Swiss-Prot), Marco Pagni (VitalIT)

#### Laboratory research:

 Franck Bontems, Marjorie Desmurs, Camille Mary, Fabiana Tirone, Rachel Porcelli, Irene Rossito and Lisa Salleron

#### Directed by:

- Amos Bairoch, Lydie Lane and Nasri Nahas



