Mining the biomedical literature for protein functions and interactions

Miguel Andrade
Computational Biology & Data Mining group
Max Delbrück Center for Molecular Medicine
miguel.andrade@mdc-berlin.de

HELMHOLTZ GEMEINSCHAFT
Open Access
(cc) BY

MedlineRanker

Jean-Fred Fontaine

Discriminative words

rank	word	weight
1	aggregation	7.00
2	synuclein	6.21
3	misfolding	5.72
4	abeta	5.43
5	lewy	5.32
6	tangle	5.14
7	alzheimer	5.09
8	neurodegeneration	4.89
9	amyloid	4.87
10	tau	4.86
11	app	4.74
12	aggregate	4.67
13	huntington	4.56
14	prion	4.44
15	fibril	4.43
16	oligomer	4.34
17	hallmark	4.27

Medline Ranker

Abstracts selection

The query topic (the training set) i

- the following PubMed query
- all the following MeSH terms
- the following list of PMIDs

protein aggregation brain

one per line

The reference (the background set) is defined by:

- the whole Medline database
- the following list of PMIDs

one per line

The abstracts to be ranked (the test set) are defined by:

- the training set
- the background set
- 10 000 randomly chosen recent abstracts
- publications of the last 1 month(s)
- the 1 -year(s) old abstracts
- the following list of PMIDs

one per line

Rank it | Reset

http://cbdm.mdc-berlin.de/tools/medlineranker/

MedlineRanker

Jean-Fred Fontaine

Rank	PMID	Abstract Title	P-value
1	22970285	Disturbed ca(2+) homeostasis increases glutaminyl cyclase expression ; connecting two early pathogenic events in Alzheimer 's disease in vitro.	9.78125e-05
2	2		
3	2		
4	2		
5	2		
6	2		
7	2		
8	2		
9	2		

HIGHLIGHTER CONTACT CBDM GROUP

Disturbed ca(2+) homeostasis increases glutaminyl cyclase expression ; connecting two early pathogenic events in Alzheimer 's disease in vitro.

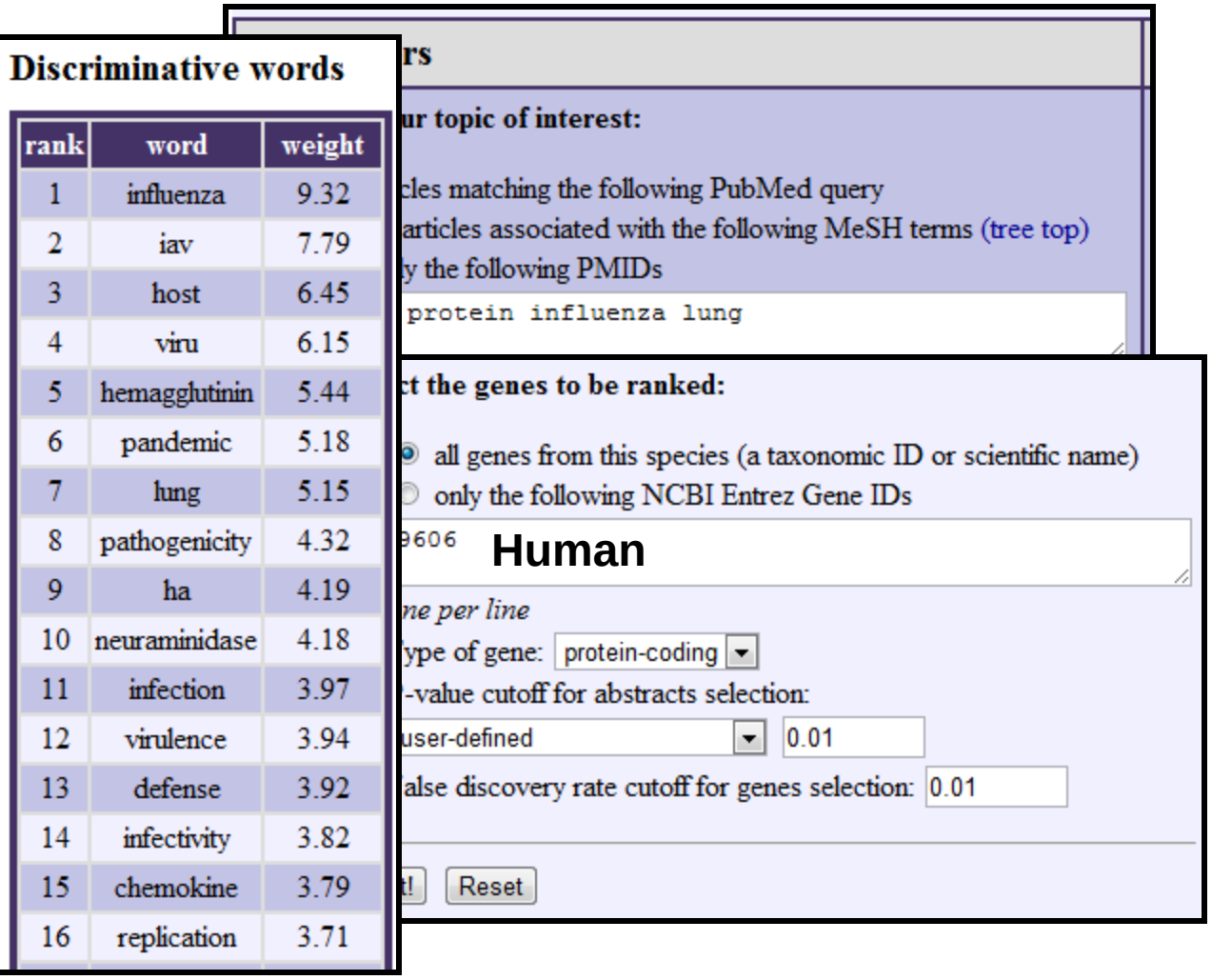
A major neuropathological hallmark of Alzheimer 's disease (AD) is the deposition of aggregated β amyloid (Aβ) peptide in the senile plaques . Aβ is a peptide of 38-43 amino acids and its accumulation and aggregation plays a key role early in the disease . A large fraction of β amyloid is N-terminally truncated rendering a glutamine that can subsequently be cyclized into pyroglutamate (pE). This makes the peptide more resistant to proteases, more prone to aggregation and increases its neurotoxicity . The enzyme glutaminyl cyclase (QC) catalyzes this conversion of glutamine to pE. In brains of AD patients, the expression of QC is increased in the earliest stages of pathology , which may be an important event in the pathogenesis . In this study we aimed to investigate the regulatory mechanism underlying the upregulation of QC expression in AD . Using differentiated SK-N-SH as a neuronal cell model , we found that neither the presence of Aβ peptides nor the unfolded protein response, two early events in AD , leads to increased QC levels . In contrast, we demonstrated increased QC mRNA levels and enzyme activity in response to another pathogenic factor in AD , perturbed intracellular Ca(2+) homeostasis. The QC promoter contains a putative binding site for the Ca(2+) dependent transcription factors c-fos and c-jun. C-fos and c-jun are induced by the same Ca(2+)-related stimuli as QC and their upregulation precedes QC expression . We show that in the human brain QC is predominantly expressed by neurons . Interestingly, the Ca(2+)- dependent regulation of both c-fos and QC is not observed in non-neuronal cells . Our results indicate that perturbed Ca(2+) homeostasis results in upregulation of QC selectively in neuronal cells via Ca(2+)- dependent transcription factors. This suggests that disruption of Ca(2+) homeostasis may contribute to the formation of the neurotoxic pE Aβ peptides in Alzheimer 's disease .

Discrim

rank	
1	a
2	
3	
4	
5	
6	
7	
8	neur
9	
10	
11	
12	
13	
14	prion
15	fibril
16	oligomer
17	hallmark

http://cbdm.mdc-berlin.de/tools/medlineranker/

Génie



Ranks a set of genes from a whole genome according to a topic

Fontaine *et al.* (2011) *Nucleic Acids Research*

http://cbdm.mdc-berlin.de/tools/genie/

Génie

Rank	GeneID	Symbol	Homologs	PMIDs	Hits	FDR	Top 10 abstracts
1	3458	IFNG					
2	7124	TNF					
3	3576	IL8					
4	3586	IL10					
5	7097	TLR2					
6	7099	TLR4					

HIGHLIGHTER CONTACT CBDM GROUP

Interferon -gamma inhibits STAT6 signal transduction and gene expression in human airway epithelial cells .

The activating and inhibitory cytokine signals that act upon epithelial cells in the human lung are critically important for controlling the production of inflammatory mediators from those cells in the context of allergic disease . The cytokines interleukin (IL)-4 and IL -13, derived from T helper (Th)-2 cells and other cell types, are potent inducers of epithelial cell expression of a host of inflammatory molecules , including the chemokines eotaxin-1, -2 and -3. Intracellular signal transduction in response to IL -4/IL -13 occurs largely through activation of signal transducer and activator of transcription 6 (STAT6). Interferon (IFN)-gamma , a Th1-type cytokine , has opposing effects to IL -4/IL -13 in various cell types, including T cells , B-cells , endothelium, and epithelium . In this study, we demonstrate that IL -4-induced STAT6 activation was inhibited profoundly by 24 h pretreatment with IFN -gamma in human primary airway epithelial cell cultures . Using Western blotting, we showed that the levels of both cytoplasmic and nuclear-localized phospho-STAT6 were reduced by IFN -gamma pretreatment, and this effect was dependent on the concentration of IFN -gamma and time of exposure to IFN -gamma . The functional activity of STAT6 was also completely inhibited by IFN -gamma : IL -4-induced luciferase activity from a STAT6-driven reporter construct was suppressed, as was IL -4-induced expression of messenger RNA (mRNA) and protein for eotaxin-3, a STAT6-dependent gene implicated in allergic inflammation . We found that mRNA for suppressor of cytokine signaling (SOCS)-1 and (SOCS)-3, known inhibitors of IL -4 signaling, and IL -13 receptor alpha2, a potential inhibitor of IL -4 signaling, were both strongly induced by IFN -gamma pretreatment. IFN -gamma also increased the rate of decay of IL -4-induced eotaxin-3 mRNA . We conclude that there are multiple mechanisms by which IFN -gamma regulates IL -4- and STAT6-dependent signaling and gene expression in airway epithelial cells . These observations have important implications for the regulation of epithelial cell activation by the balance of Th1/Th2-type cytokines in the airways in allergic disease .

http://cbdm.mdc-berlin.de/tools/genie/

PESCADOR

Adriano Barbosa

PESCADOR

Platform for Exploration of Significant Concepts AssociateD to co-Occurrences Relationships.

Input | Concepts | Retrieval | Development | Help

MDC Berlin-Buch

INPUT **[Required]**

Paste below your list of PubMed IDs (one per line!):

```
17151287
18561034
17259179
12147333
15916898
18585350
15710903
19422822
```

Example: Alzheimer and Parkinson diseases i

Other examples of PMIDs lists related to:
Phosphorylation in Yeast
Host-Pathogen Interactions in *Arabidopsis t*
Cell Cycle in *Escherichia coli*

Clear

Target Species

Inform below the NCBI's Taxonomy ID for t

9606

Examples: 9606 (*H. sapiens*), 3702 (*A. thal*

PLUS

Customized concepts

Load below the biological concepts to be checked for (one per line!)

```
ALZHEIMER
AD
PARKINSON
PD
AGGREGATION
AMYLOID
CLEAVAGE
```

Example Clear

Start analysis

Extract interactions and filter by concepts

Barbosa-Silva et al. (2010) *BMC Bioinformatics*

Barbosa-Silva et al. (2011) *BMC Bioinformatics*

http://cbdm.mdc-berlin.de/tools/pescador/

PESCADOR

PESCADOR

Platf

Target Organism: *Homo sapiens* (TAXID: 9606)

Click on a co-occurrence type to filter the type of co-occurrences displayed.

Selected PubMed ID: 10764738

Sentence 1: **Microtubule-associated protein 1B is a component of cortical Lewy bodies and binds alpha-synuclein filaments.**

Sentence 2: Lewy bodies, neuropathological hallmarks of Parkinson's disease and dementia with Lewy bodies, comprise alpha-synuclein filaments and other less defined proteins.

Sentence 3: Characterization of Lewy body proteins that interact with alpha-synuclein may provide insight into the mechanism of Lewy body formation.

Sentence 4: Double immunofluorescence labeling and confocal microscopy revealed approximately 80% of cortical Lewy bodies contained microtubule-associated protein 1B (MAP-1B) that overlapped with alpha-synuclein.

Sentence 5: Lewy bodies were isolated using an immunomagnetic technique from brain tissue of patients dying with dementia with Lewy bodies.

Sentence 6: Lewy body proteins were resolved by polyacrylamide gel electrophoresis.

Sentence 7: Immunoblotting confirmed the presence of MAP-1B and alpha-synuclein in purified Lewy bodies.

Sentence 8: Direct binding studies revealed a high affinity interaction (IC(50) approximately 20 nm) between MAP-1B and alpha-synuclein.

Sentence 9: The MAP-1B-binding sites were mapped to the last 45 amino acids of the alpha-synuclein C terminus.

Sentence 10: MAP-1B also bound in vitro assembled alpha-synuclein fibrils.

Sentence 11: Thus, MAP-1B may be involved in the pathogenesis of Lewy bodies via its interaction with monomeric and fibrillar alpha-synuclein.

PESCADOR

Type 1

MAP-1B also bound in vitro assembled alpha-synuclein fibrils.

Term + [Biointeraction] + Term

Type 2

Direct binding studies revealed a high affinity interaction (IC(50) approximately 20 nm) between MAP-1B and alpha-synuclein.

[Biointeraction] +Term + Term + [Biointeraction]

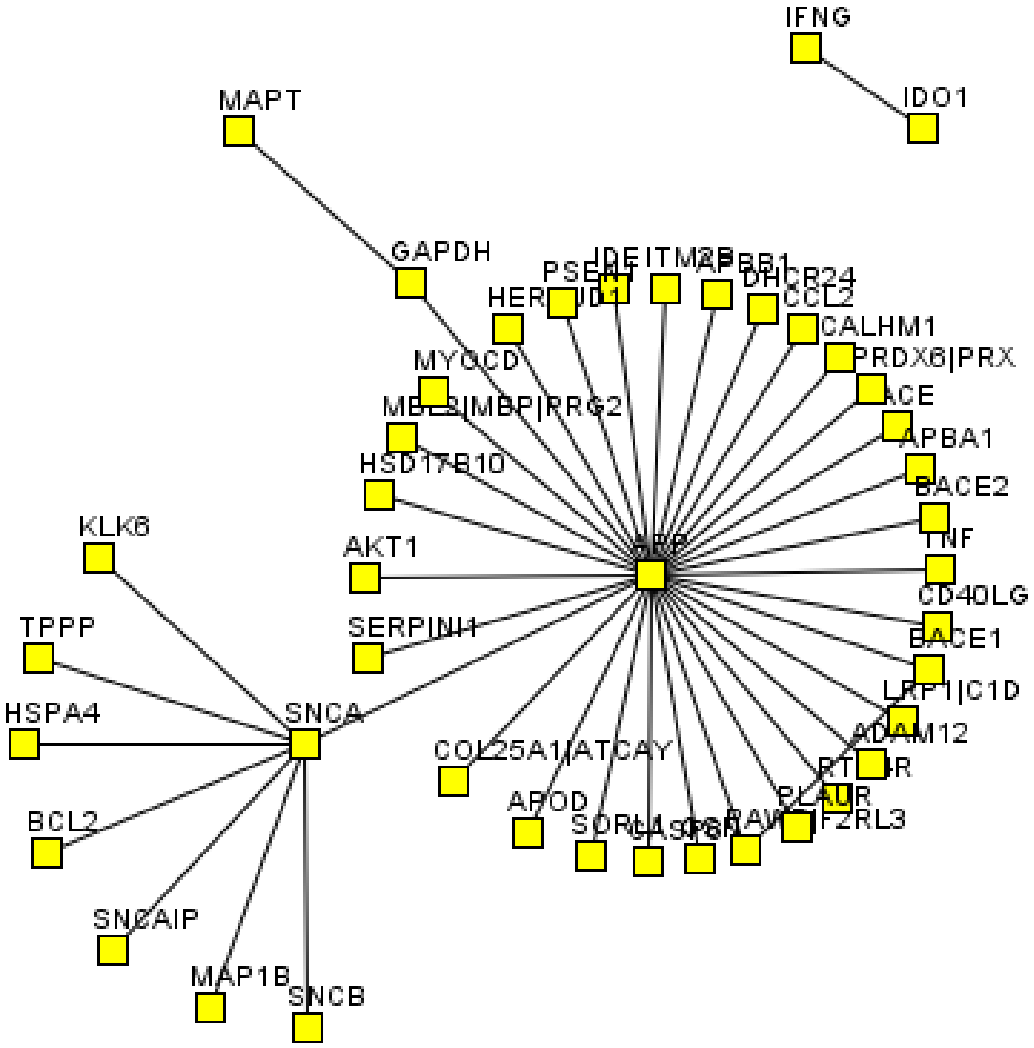
Type 3

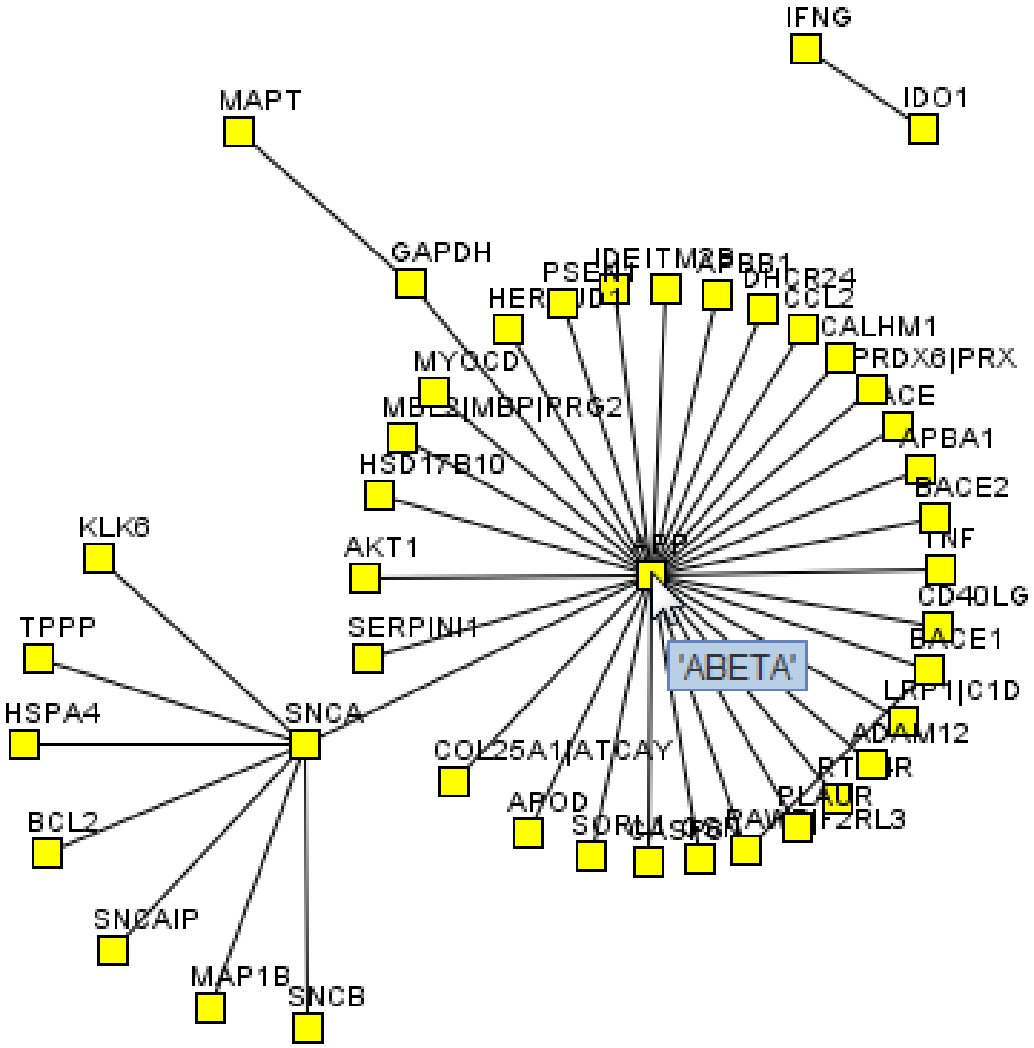
Immunoblotting confirmed the presence of MAP-1B and alpha-synuclein in purified Lewy bodies.

Term + Term

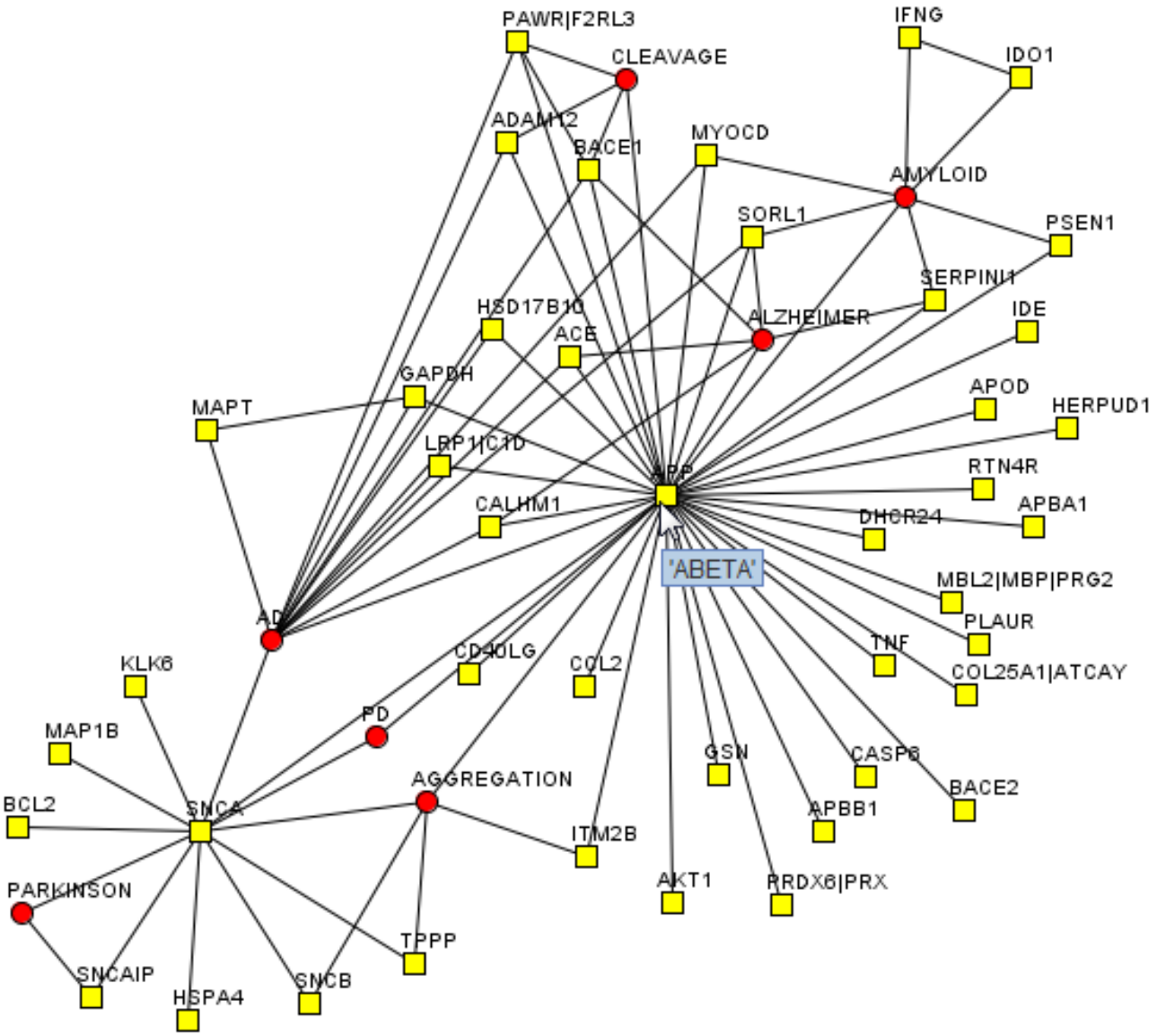
Type 4

co-occurrence in abstract


IFNG
IDO1
MAPT
GAPDH
DHCR24
CCL2
CALHM1
MYOCD
HSD17B10
APBA1
BACE2
TNF
KLK6
AKT1
CD40LG
TPPP
SERPINH1
BACE1
HSPA4
SNCA
LRP1|C1D
ADAM12
COL25A1|ATCAY
APOD
PLAUR
BCL2
SNCAIP
MAP1B
SNCB


IFNG
IDO1
MAPT
GAPDH
CALHM1
MYOCD
HSD17B10
AKT1
TNF
CD40LG
BACE1
'ABETA'
TPPP
SERPINH1
HSPA4
SNCA
KLK6
BCL2
SNCAIP
MAP1B
SNCB

Sentence 4: Functionally, purified recombinant human p25alpha strongly stimulates the AGGREGATION of alpha-synuclein in vitro as demonstrated by thioflavin-T fluorescence and quantitative electron microscopy.



MLTrends

Graph historical term usage in MEDLINE

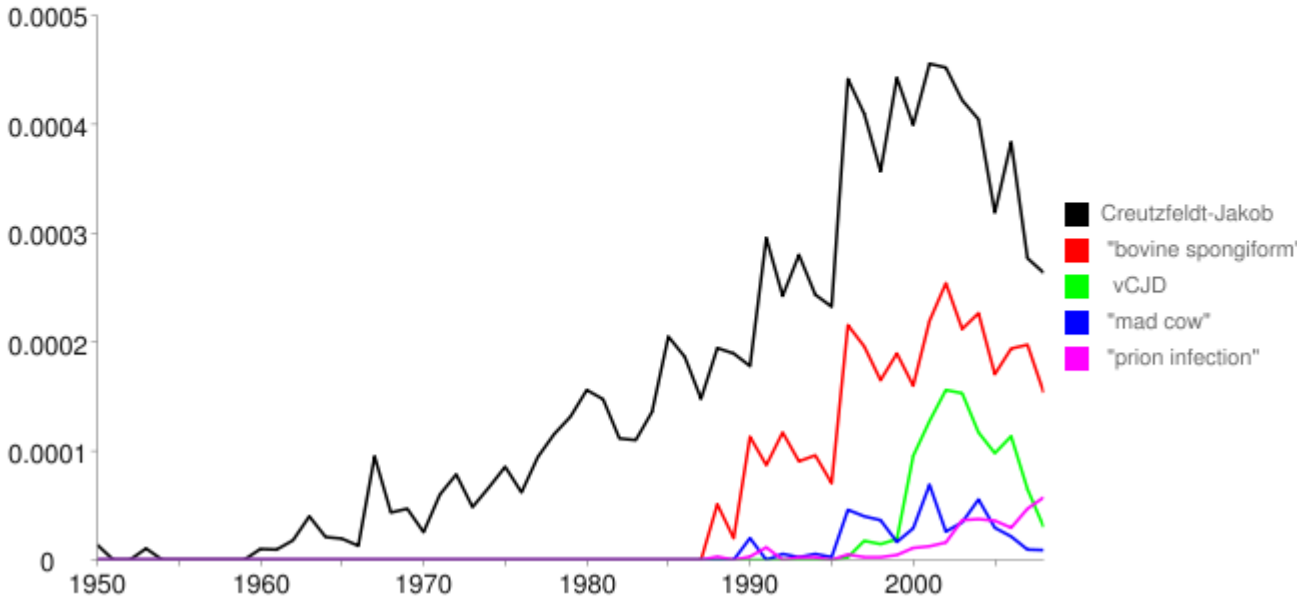
http://www.ogic.ca/mltrends/

Gareth Palidwor
(OHRI-Ottawa)

MLTrends

search in: titles and abstracts | normalization: publications | scale: linear

Creutzfeldt-Jakob, "bovine spongiform", vl Graph! ?



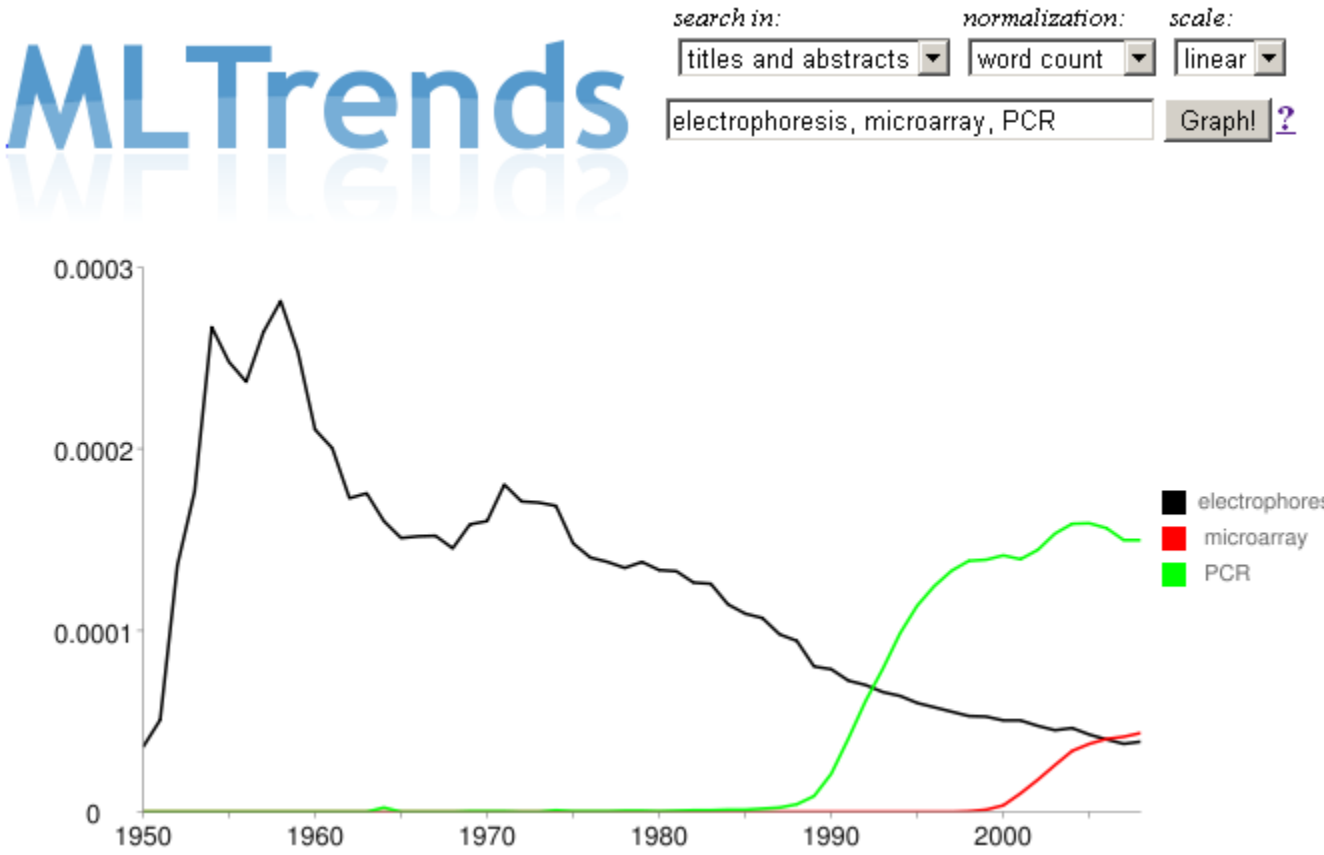
Palidwor and Andrade-Navarro (2010) *Journal of Biomedical Discovery and Collaboration*

MLTrends

Graph historical term usage in MEDLINE

http://www.ogic.ca/mltrends/

Gareth Palidwor
(OHRI-Ottawa)



Palidwor and Andrade-Navarro (2010) *Journal of Biomedical Discovery and Collaboration*

MLTrends

Graph historical term usage in MEDLINE

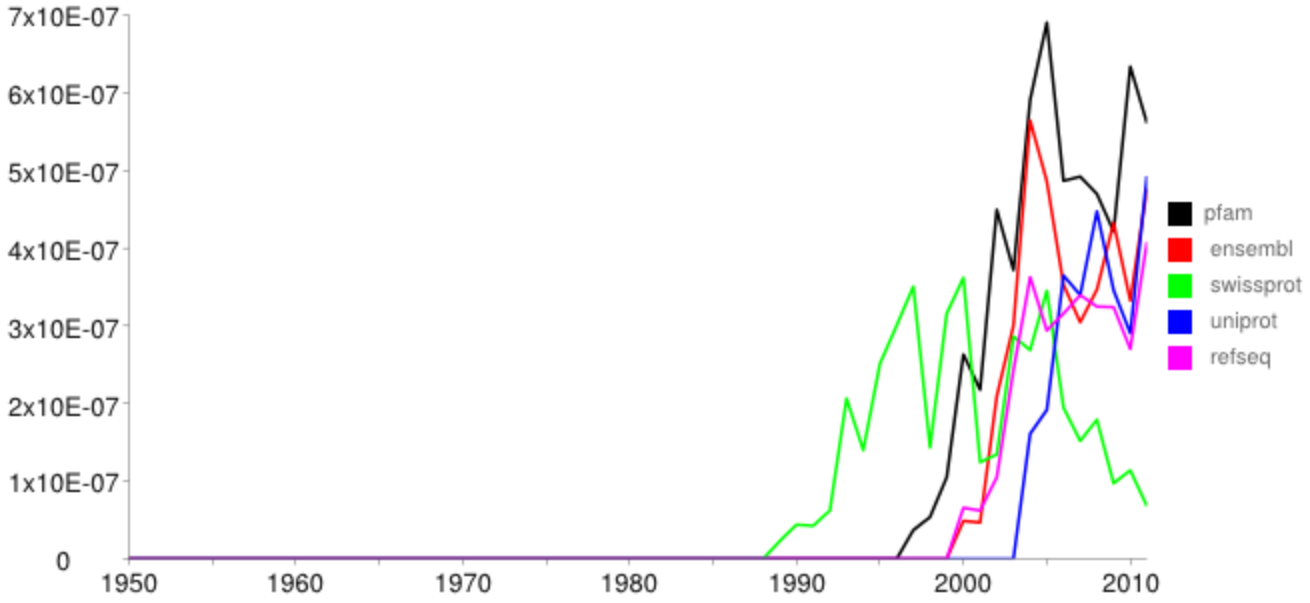
http://www.ogic.ca/mltrends/

Gareth Palidwor
(OHRI-Ottawa)

MLTrends

search in: titles and abstracts | normalization: word count | scale: linear

pfam, ensembl, swissprot, uniprot, refseq | Graph! | ?



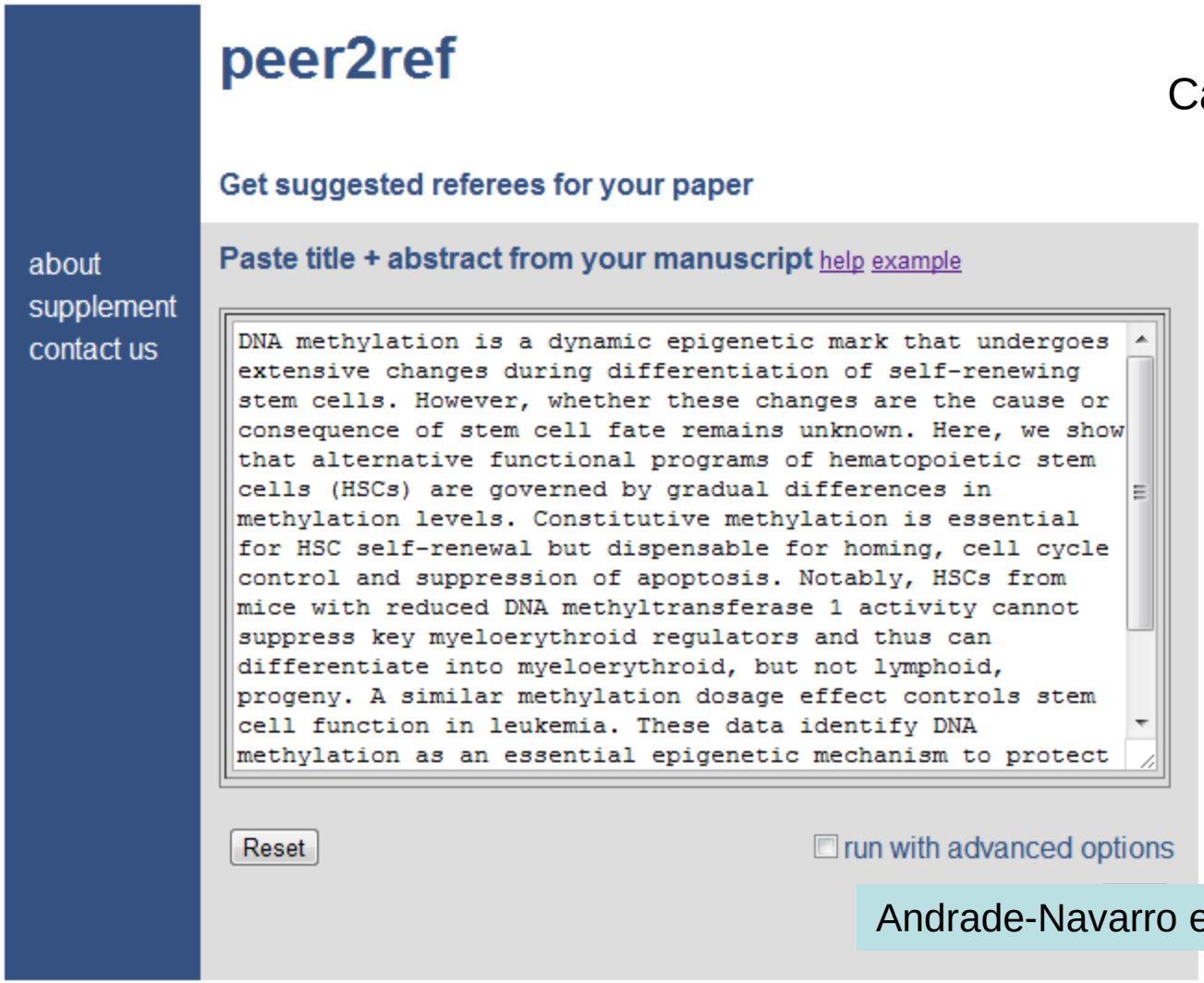
Palidwor and Andrade-Navarro (2010) *Journal of Biomedical Discovery and Collaboration*

peer2ref

Find referees

http://www.ogic.ca/projects/peer2ref/

Carolina Perez-Iratxeta
(OHRI-Ottawa)



Andrade-Navarro et al (2012) *BioData Mining*

peer2ref

Find referees

http://www.ogic.ca/peer2ref/

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

home
about
suppl
conta

Display Settings: Summary, Sorted by Recently Added

Send to:

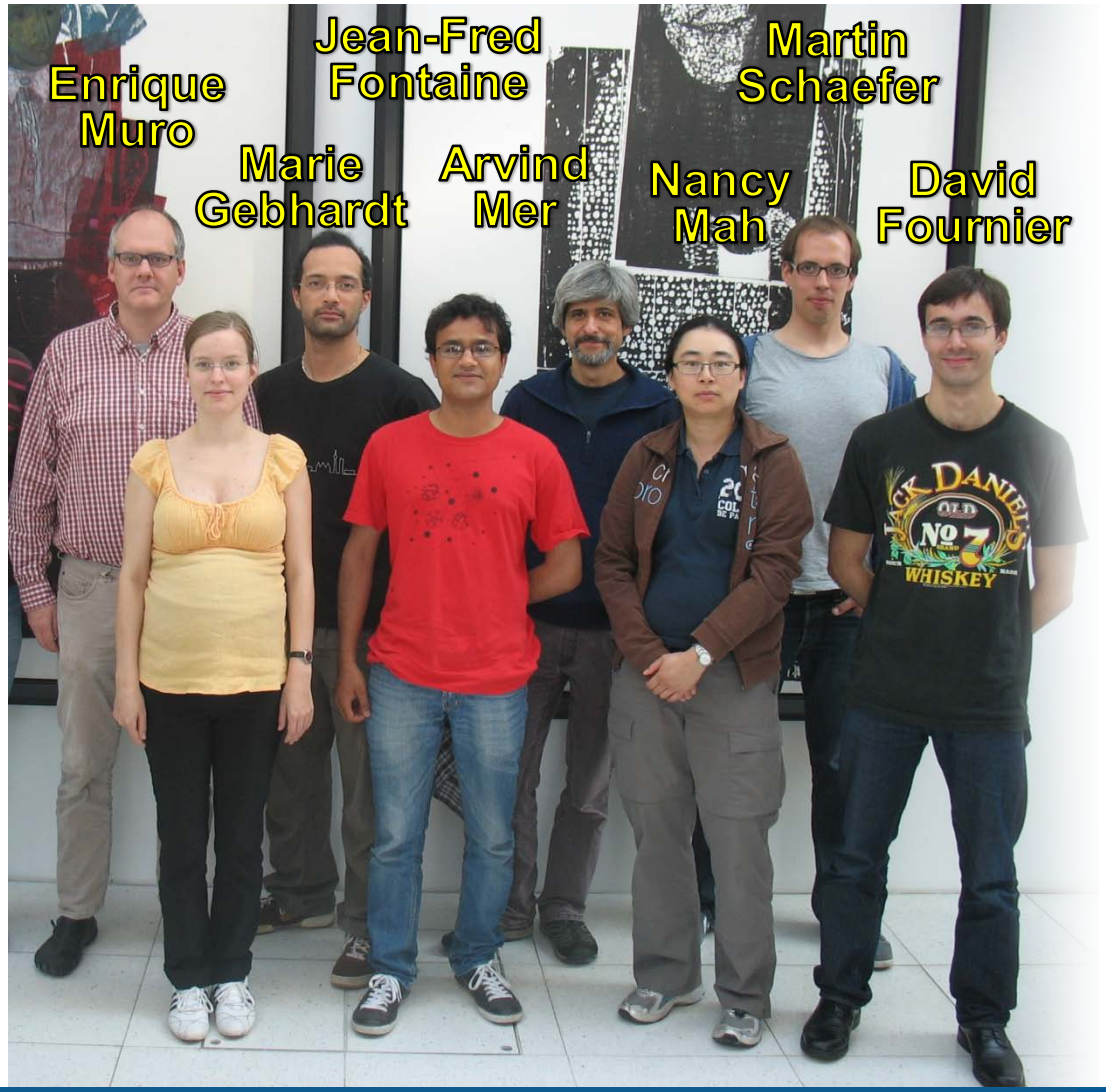
Results: 5

1. IFN-gamma negatively modulates self-renewal of repopulating human hemopoietic stem cells.
Yang L, Dybedal I, Bryder D, Nilsson L, Sitnicka E, Sasaki Y, Jacobsen SE.
J Immunol. 2005 Jan 15;174(2):752-7.
PMID: 15634895 [PubMed - indexed for MEDLINE] Free Article
Related citations

2. Molecular evidence for hierarchical transcriptional lineage priming in fetal and adult stem cells and multipotent progenitors.
Månsson R, Hultquist A, Luc S, Yang L, Anderson K, Kharazi S, Al-Hashmi S, Liuba K, Thorén L, Adolfsson J, Buza-Vidas N, Qian H, Soneji S, Enver T, Sigvardsson M, Jacobsen SE.
Immunity. 2007 Apr;26(4):407-19. Epub 2007 Apr 12.
PMID: 17433729 [PubMed - indexed for MEDLINE]
Related citations

3. Identification of Lin(-)Sca1(+)kit(+)CD34(+)Flt3- short-term hematopoietic stem cells capable of rapidly reconstituting and rescuing myeloablated transplant recipients.
Yang L, Bryder D, Adolfsson J, Nygren J, Månsson R, Sigvardsson M, Jacobsen SE.
Blood. 2005 Apr 1;105(7):2717-23. Epub 2004 Nov 30.
PMID: 15572596 [PubMed - indexed for MEDLINE] Free Article
Related citations

Computational Biology and Data Mining group



HELMHOLTZ ASSOCIATION

Alliance on Systems Biology

Bundesministerium für Bildung und Forschung

NGFN Nationales Genomforschungsnetz

Deutsche Forschungsgemeinschaft DFG

http://cbdm.mdc-berlin.de/

MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN BERLIN-BUCH IN DER HELMHOLTZ-GEMEINSCHAFT e.V.