Malattie autoimmuni
&
Malattie Neurodegenerative

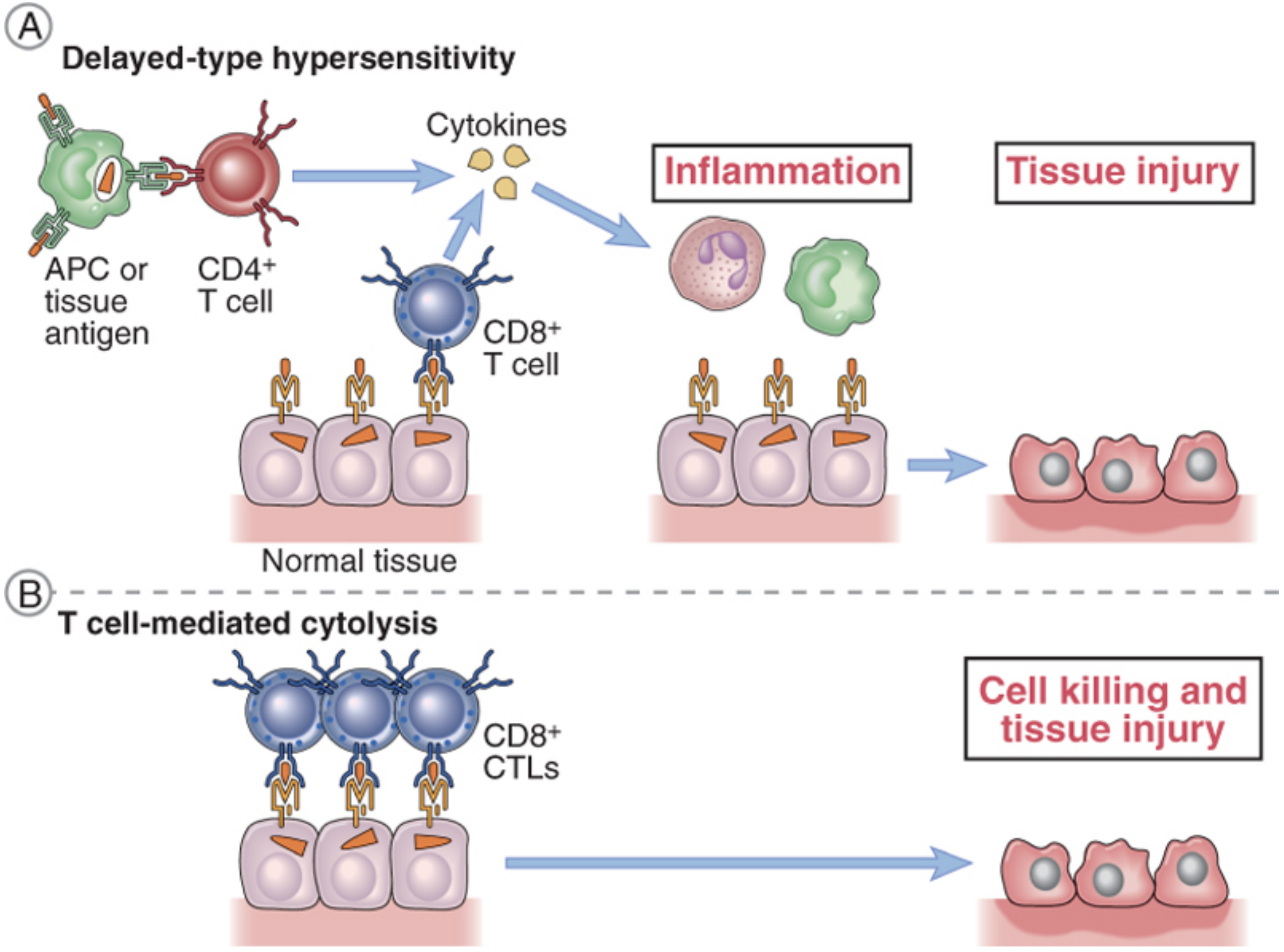
Autoimmune diseases of the central nervous system

Immunological tolerance is defined as **unresponsiveness** of the adaptive immune system to an antigen.

Tolerance to self antigens is a <u>normal feature</u> of the adaptive immune system

Failure of self tolerance results in immune reactions against self (autologous) antigens - destruction of self tissues - **AUTOIMMUNITY**

Failure of self tolerance results in immune reactions against self (autologous) antigens - destruction of self tissues - **AUTOIMMUNITY**



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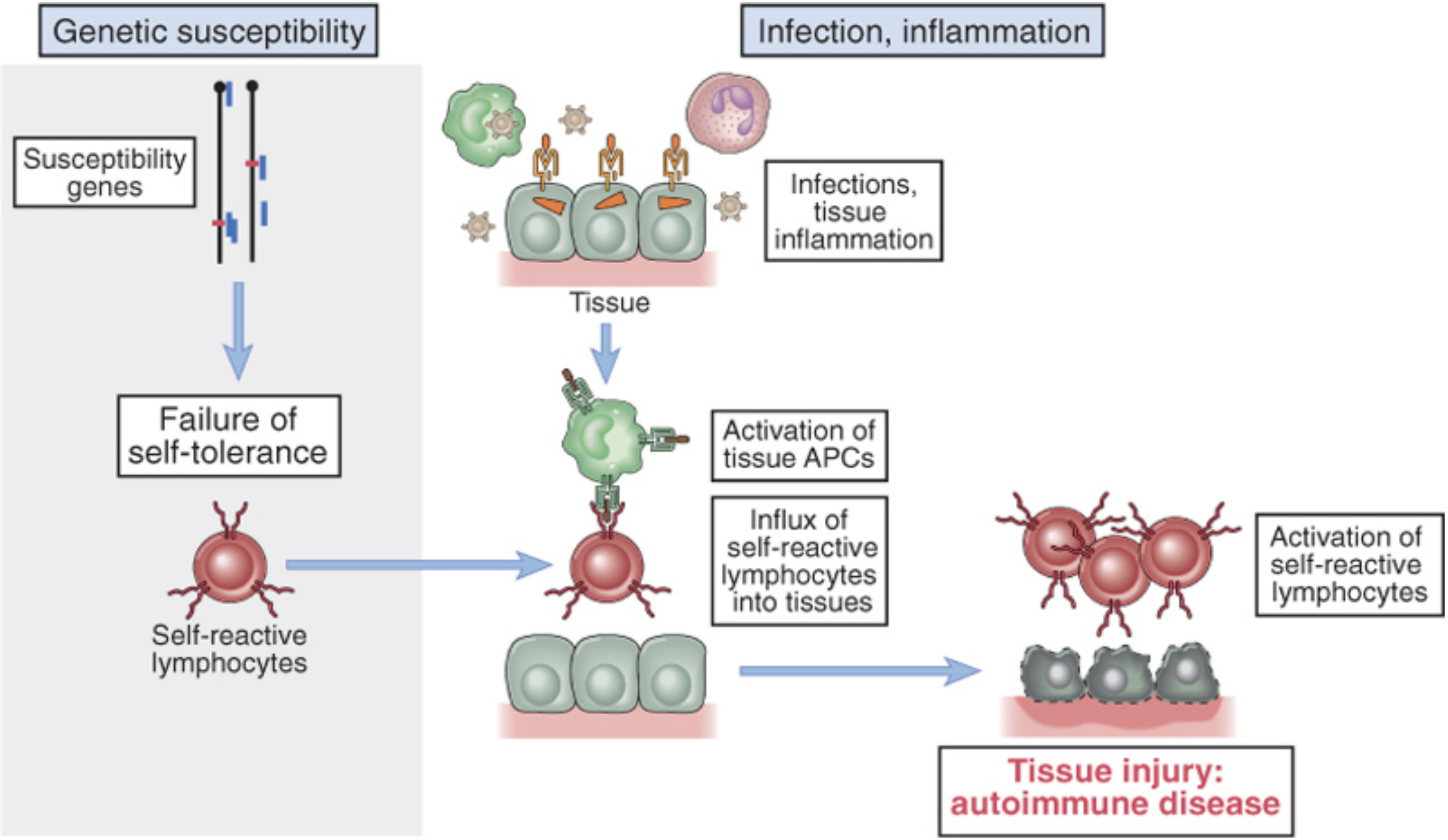
Postulated mechanisms of autoimmunity



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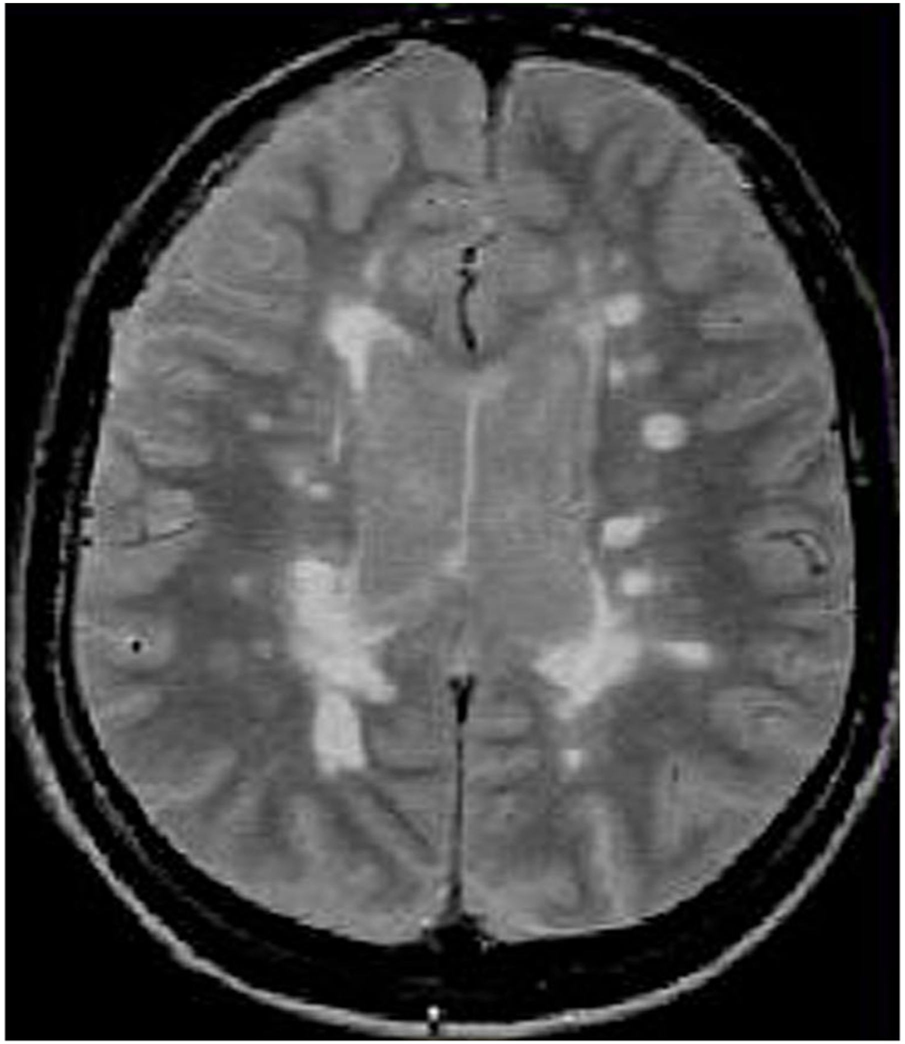
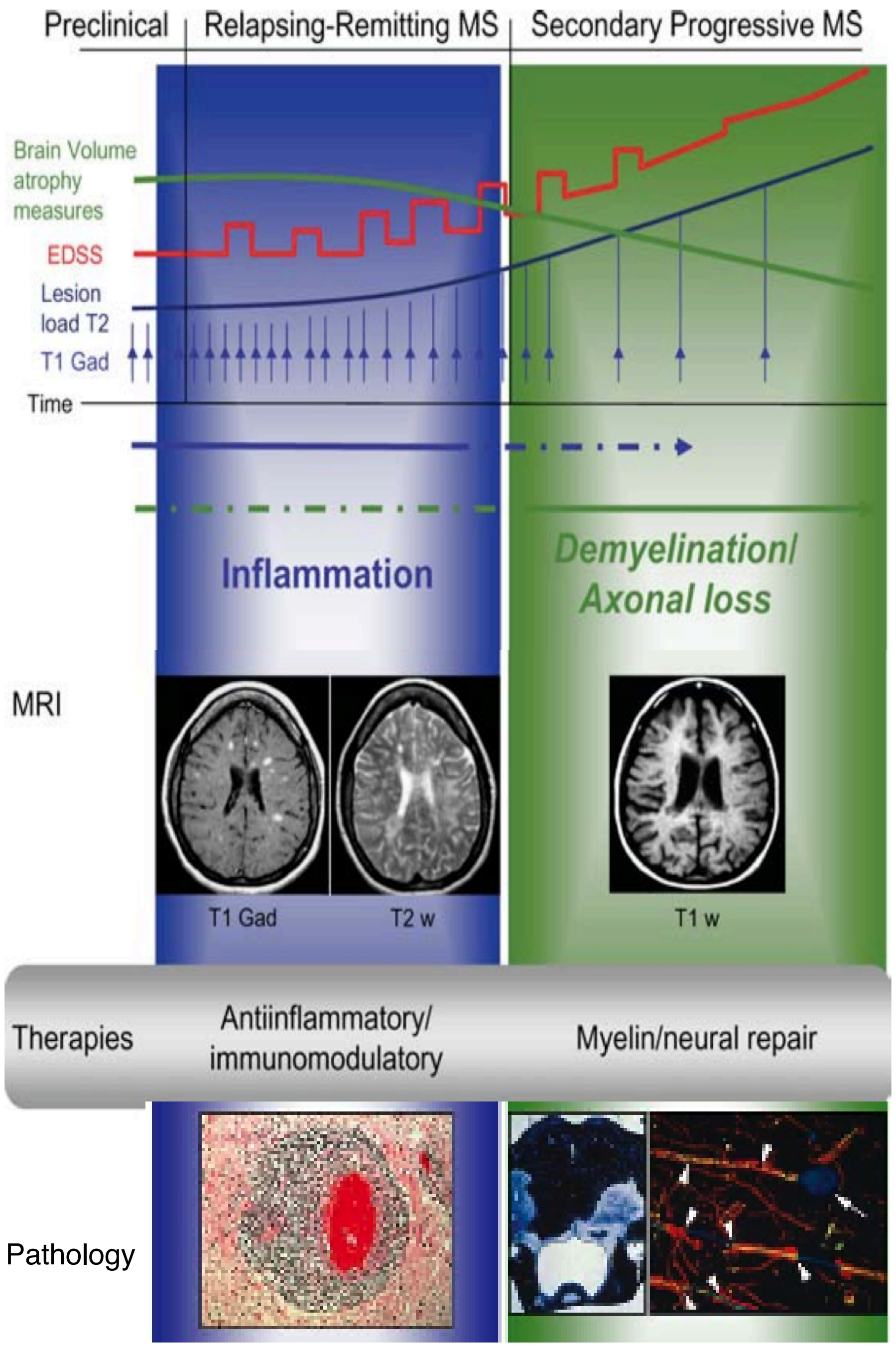
SCLEROSI MULTIPLA



85% relapsing remitting (ricadute-remissioni)

15% cronica progressiva primaria

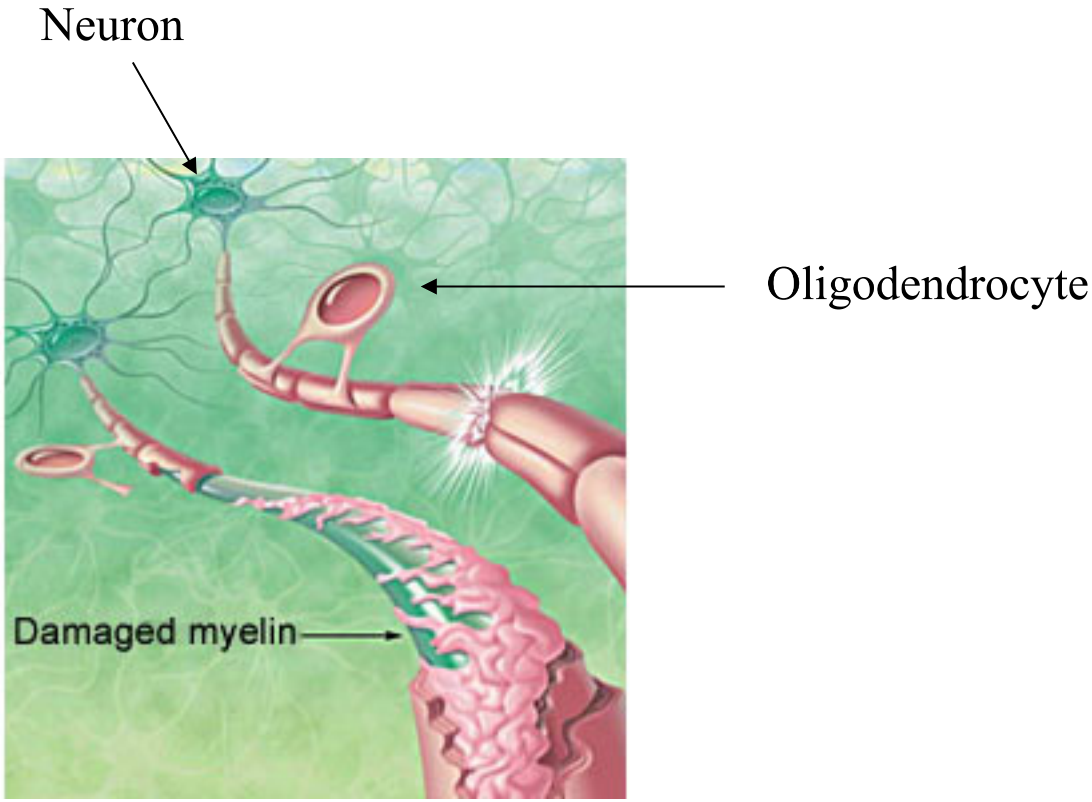
Multiple sclerosis: clinical and neuropatological characteristicts



Modified from Sospedra M, Ann Rev Immunol, 2005

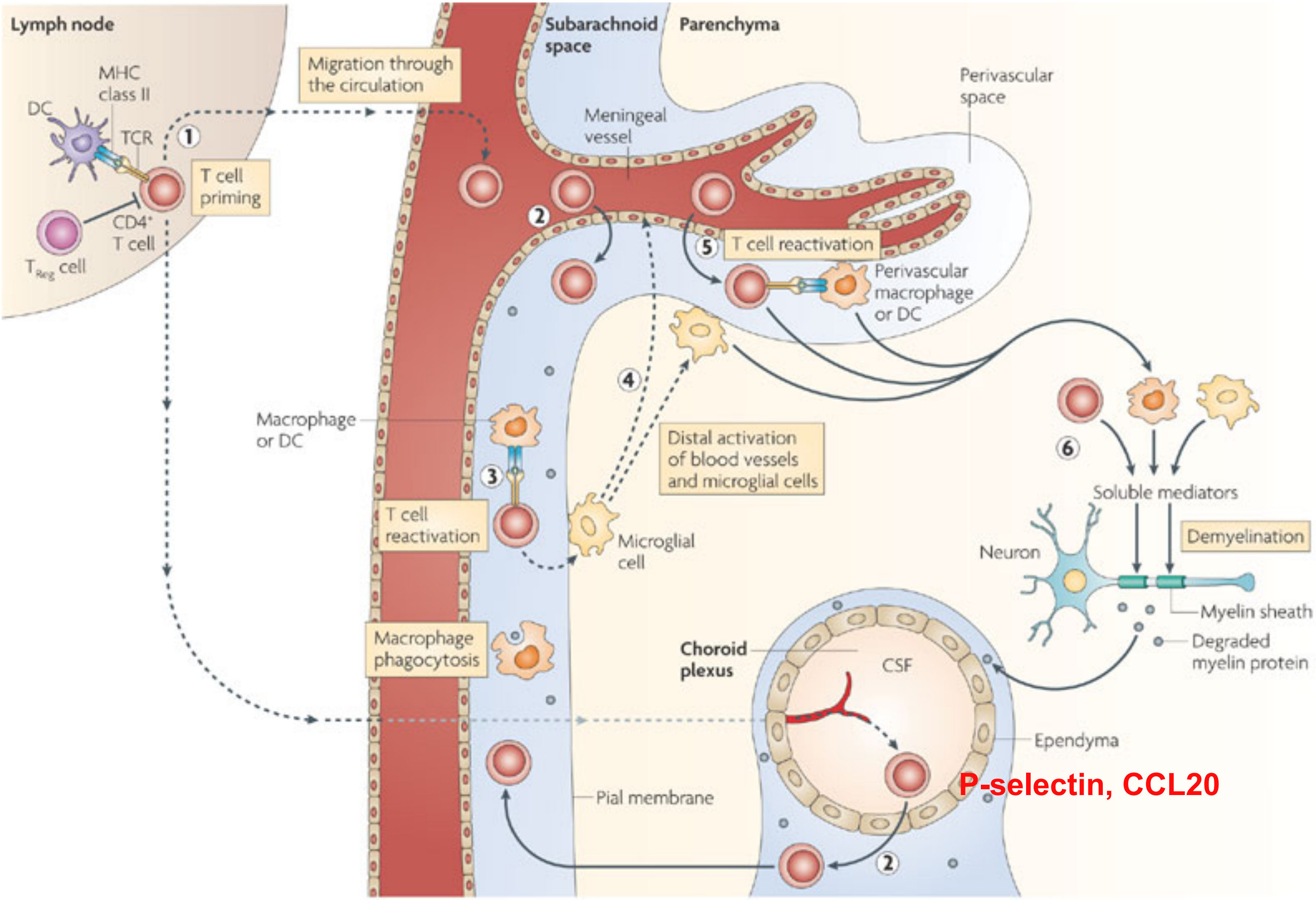
MULTIPLE SCLEROSIS (MS)

Oligodendrocyte, a principal target of immune attack in MS, synthesises and maintains the **myelin sheath** of nerve axons in the CNS



Key events in CNS autoimmunity

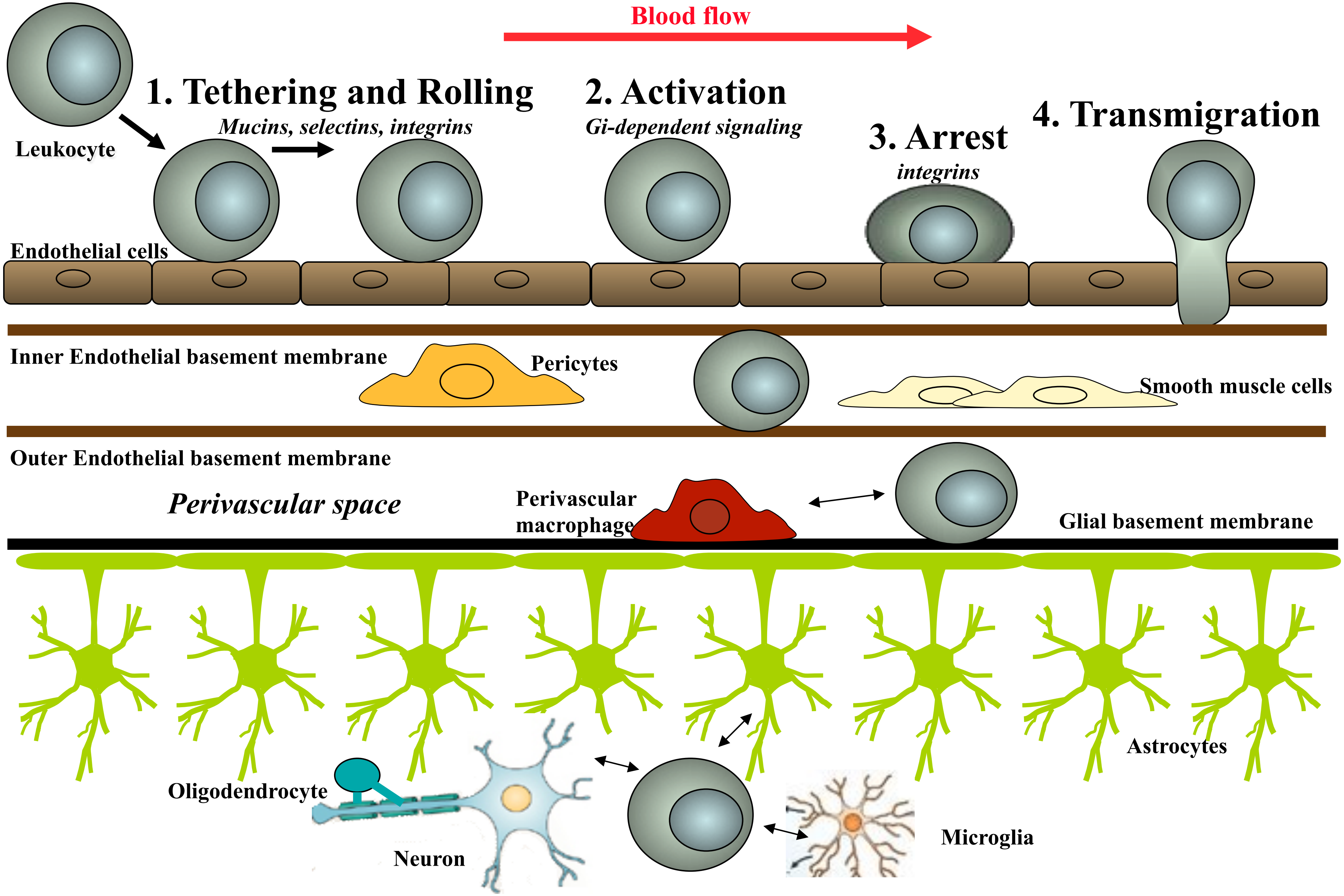
1. Activation of myelin-specific T cells in periphery
2. Migration of autoreactive T cells in the SAS
3. Reactivation of T cells in the CNS (SAS)
4. Migration into the parenchima
5. Reactivation of T cells in the parenchyma
6. Secretion of soluble mediators and brain damage



P-selectin, CCL20

Nature Reviews | Immunology

Migration of leukocytes into the central nervous system (CNS)

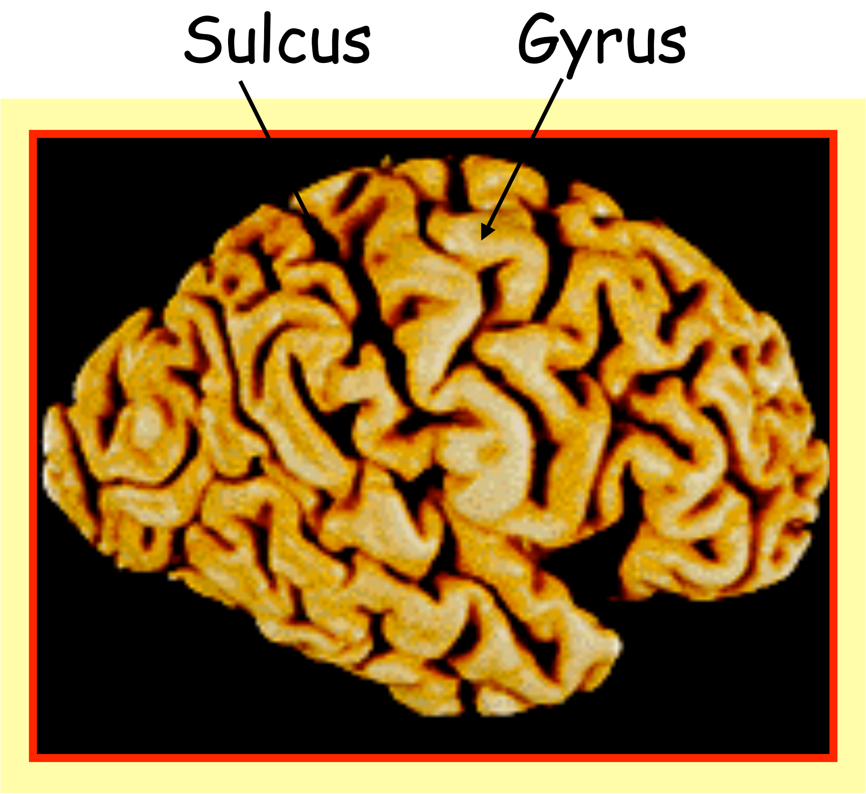


La malattia di Alzheimer

E’ una malattia neurodegenerativa progressiva caratterizzata dalla perdita di funzione e morte neuronale in diverse aree del cervello che porta alla perdita di funzioni cognitive come la memoria e l’apprendimento.

La malattia di Alzheimer è una malattia degenerativa della corteccia cerebrale

Normal Aged Brain

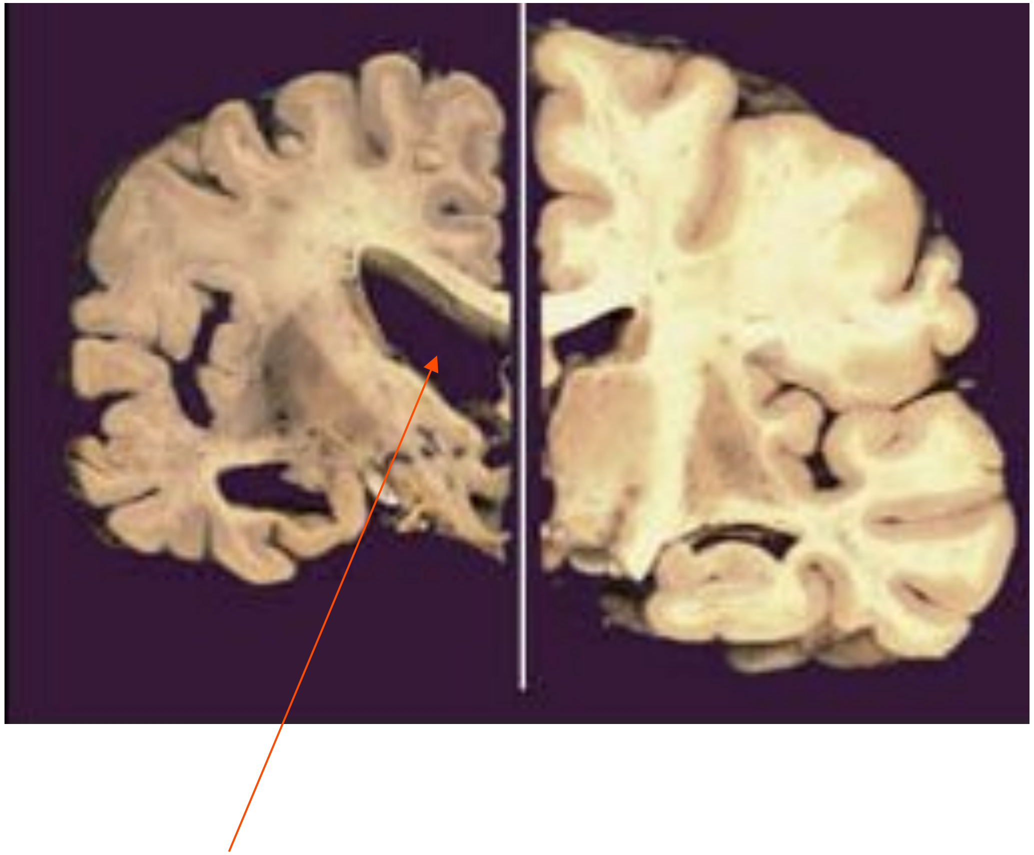


Severe AD Brain

1) Riduzione del volume del cervello
2) Allargamento dei solchi
3) Assottigliamento dei giri

} perdita di neuroni

La malattia di Alzheimer è una malattia degenerativa della corteccia cerebrale e strutture subcorticali



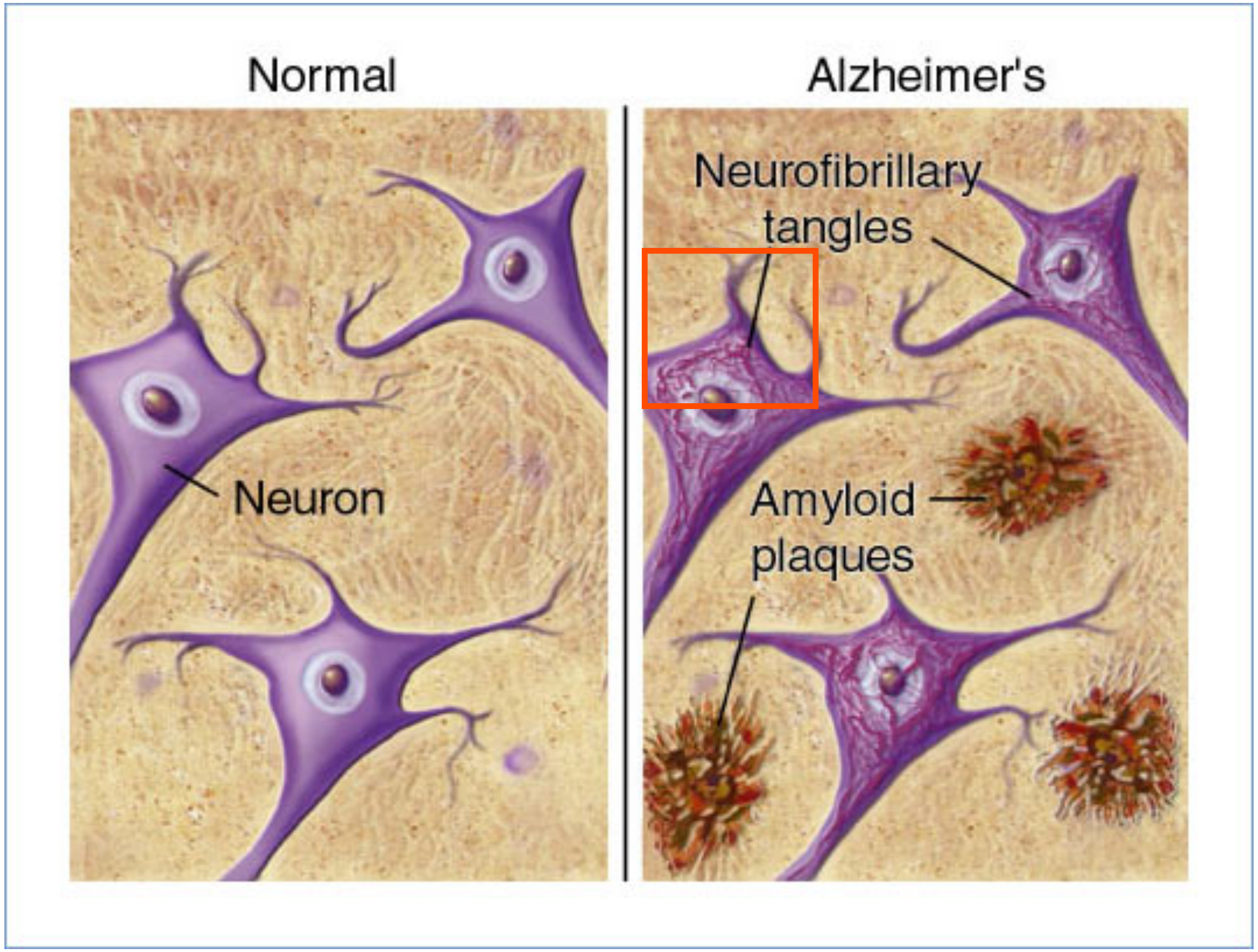
Malato

Sano

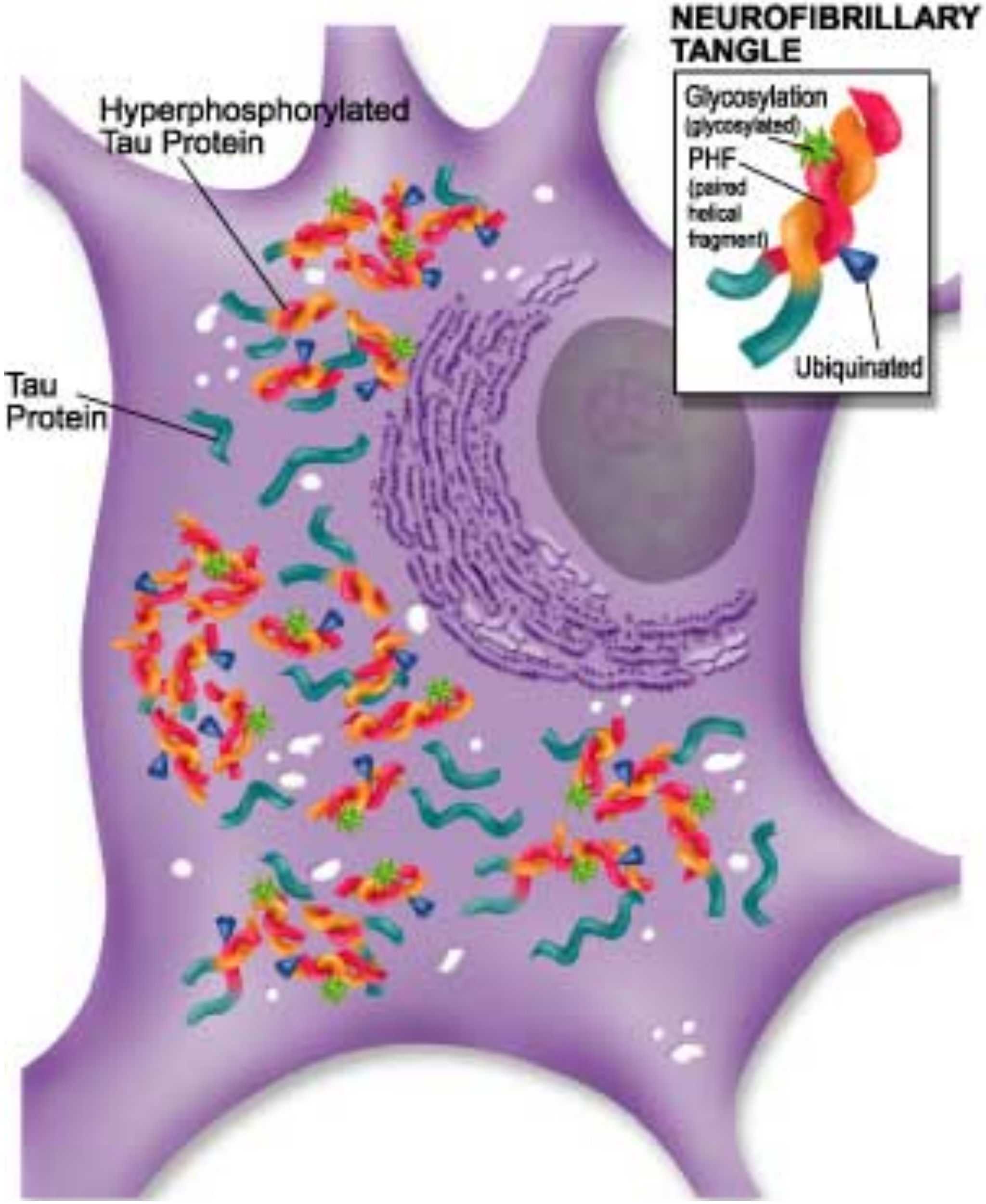
Allargamento compensatorio dei ventricoli

Caratteristiche neuropatologiche:

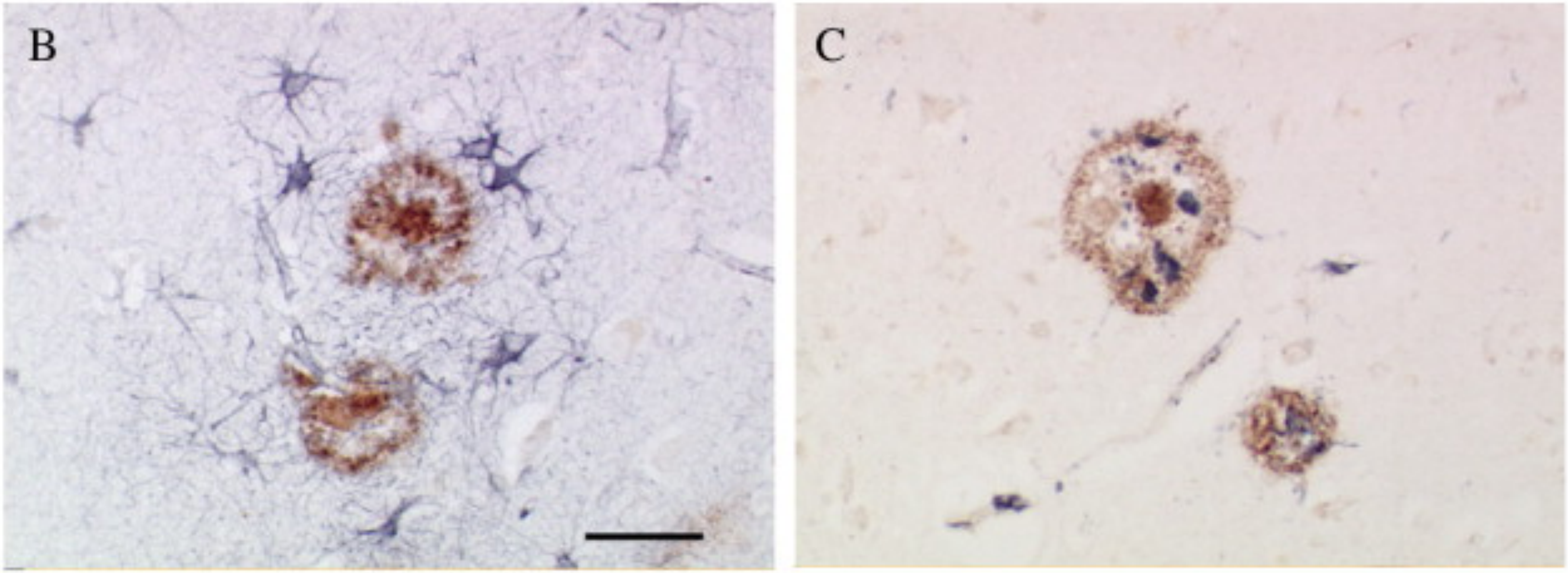
I grovigli neurofibrillari



I grovigli neurofibrillari

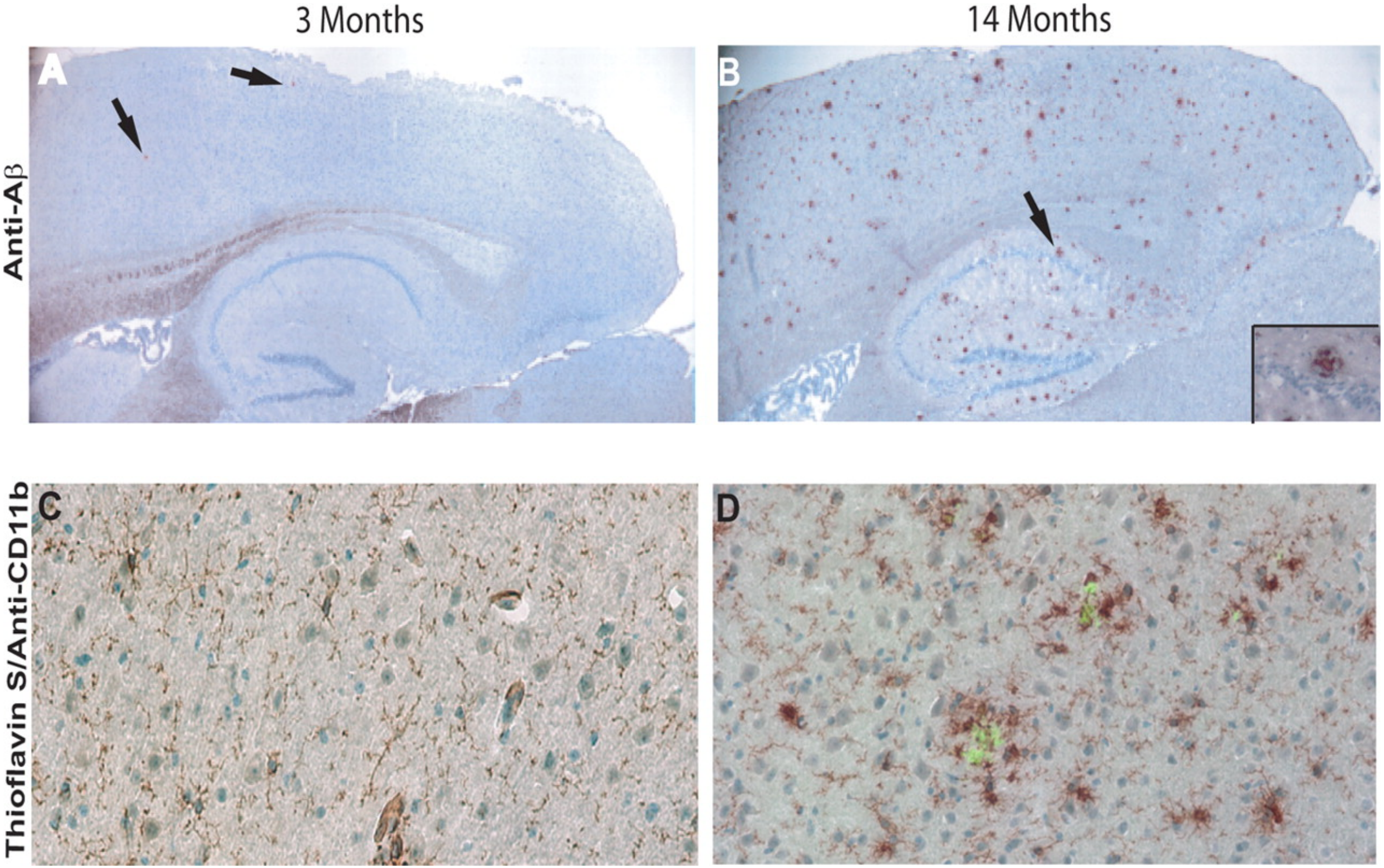


Caratteristiche neuropatologiche:
Activation of glial cells at sites of β-amyloid deposition in human brain

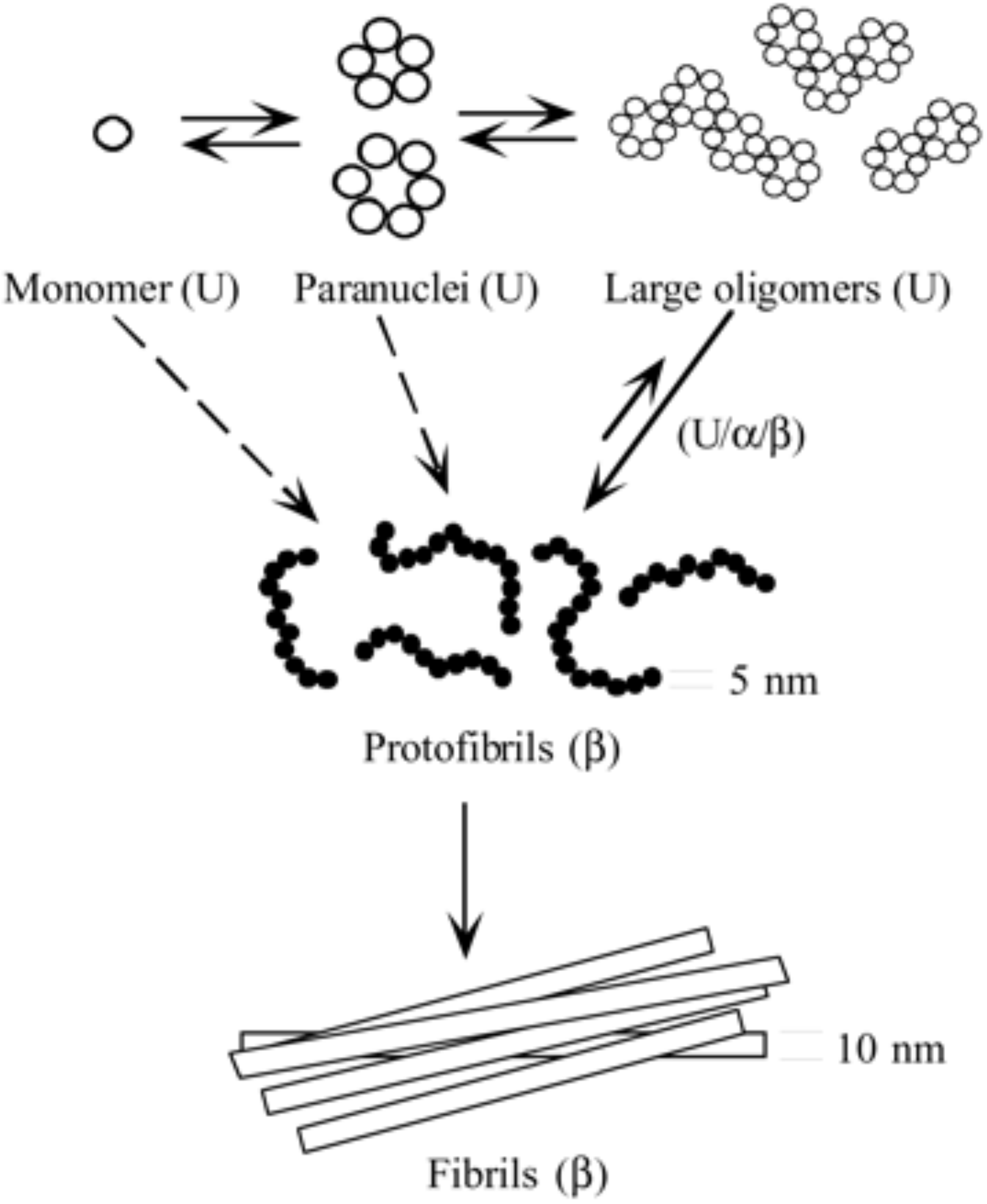


Heneka MT Brain Res. Rev. 2009

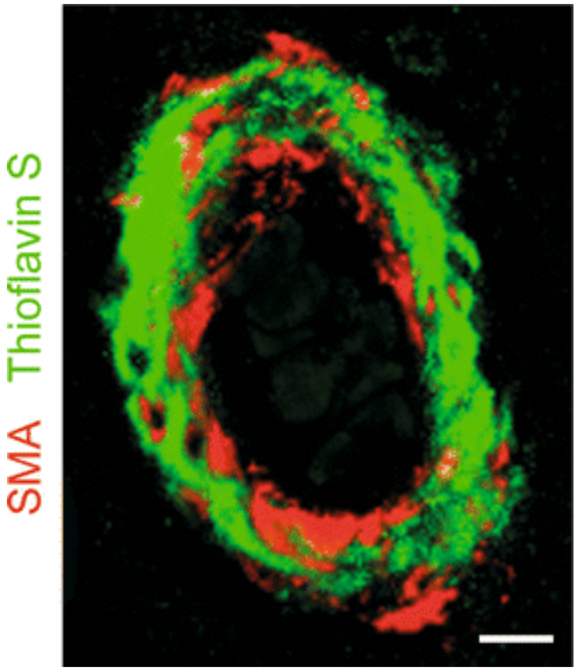
Aumento di placche di amiloide con l'età in un modello animale di malattia di Alzheimer



Modello di assemblaggio di Aβ1-42
Bitan G. PNAS 2003: 100, 330-335

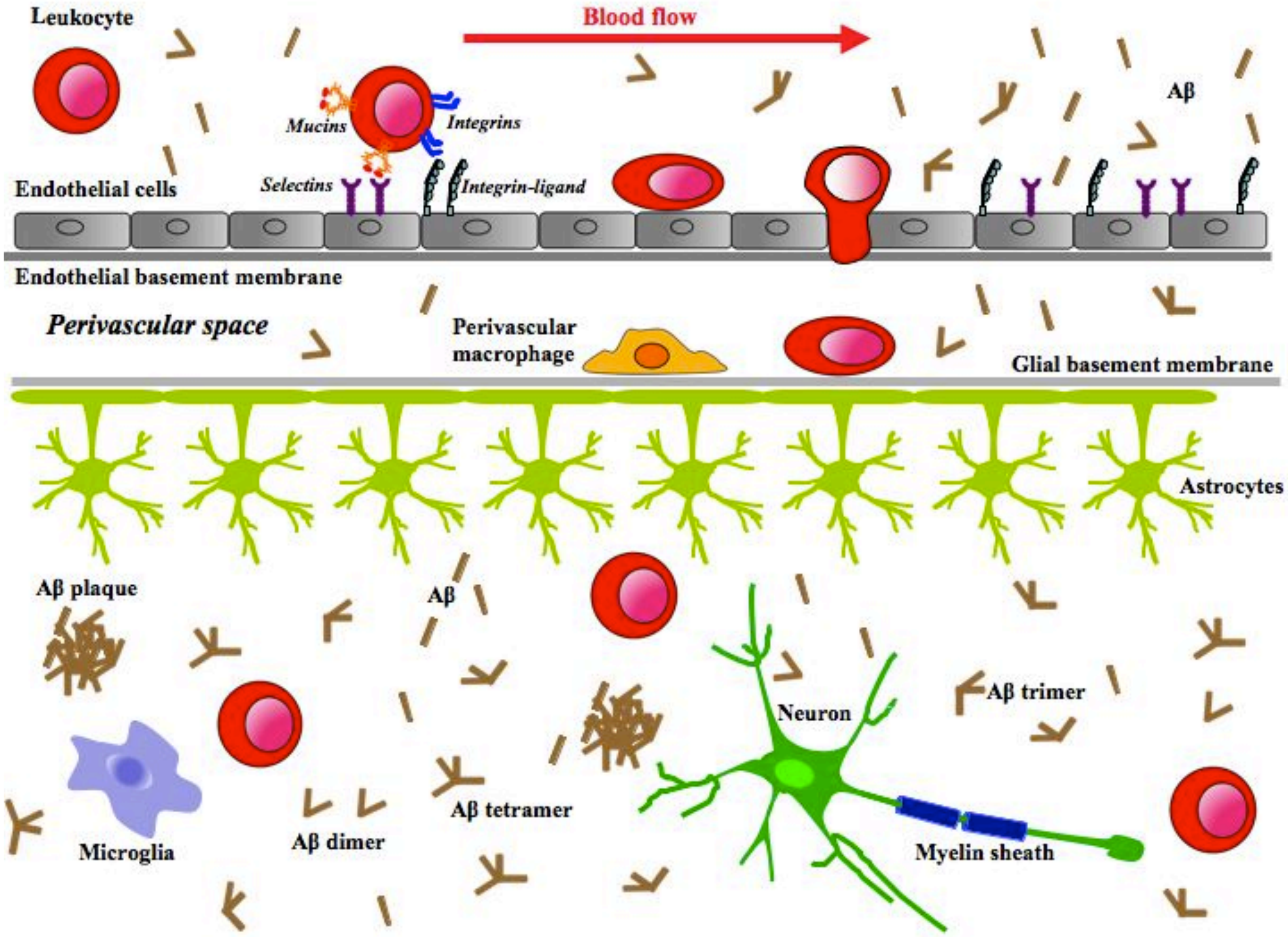


Cerebral amyloid angiopathy in AD.



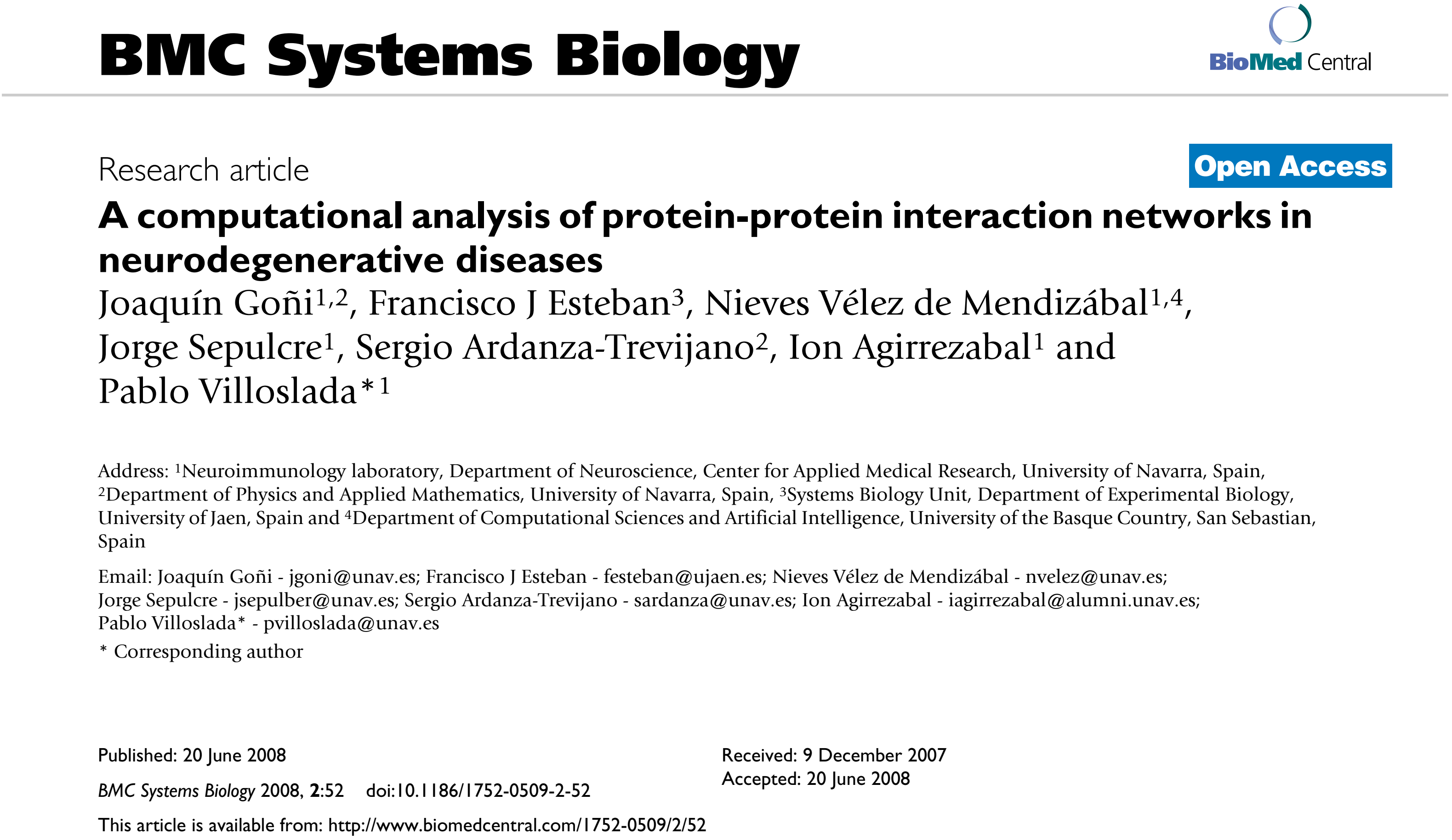
Immunofluorescent staining of smooth muscle a actin (SMA; *red*) and amyloid staining (thioflavin S, *green*) in an AD cerebral vessel

L’infiammazione vascolare e la migrazione dei leucociti hanno un ruolo nella malattia di Alzheimer



Applicazione:

Analisi computazionale delle interazioni proteina-proteina nelle malattie autoimmuni e neurodegenerative



BMC Systems Biology

BioMed Central

Research article

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A computational analysis of protein-protein interaction networks in neurodegenerative diseases

Joaquín Goñi[1,2], Francisco J Esteban[3], Nieves Vélez de Mendizábal[1,4], Jorge Sepulcre[1], Sergio Ardanza-Trevijano[2], Ion Agirrezabal[1] and Pablo Villoslada*[1]

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Accepted: 20 June 2008

Fasi dell’applicazione:

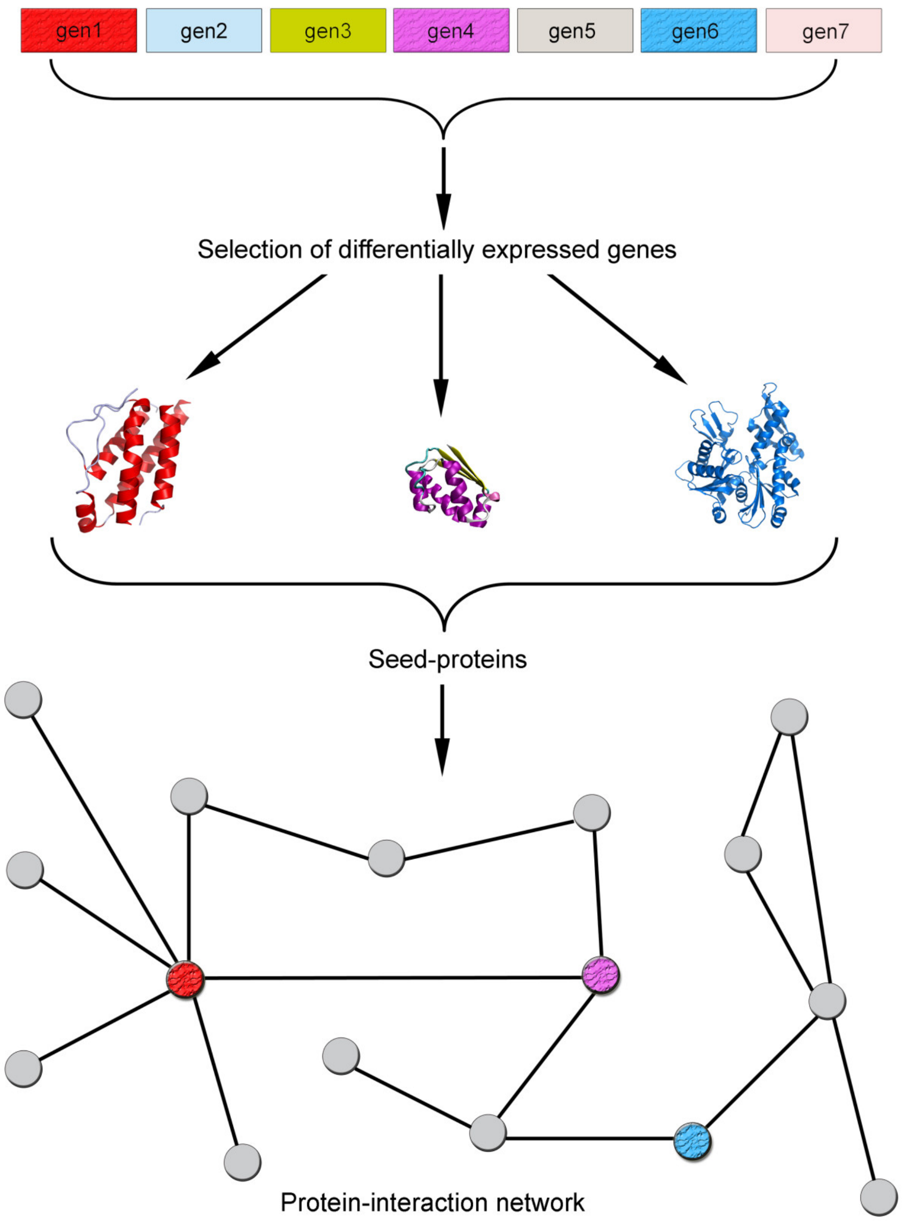
1. Ottenimento di dati sperimentali di microarrays e selezione di geni espressi differenzialmente nei pazienti

2. Costruzione di network di interazioni proteina-proteina

3. Analisi dei networks

4. Conclusioni

Lo schema dello studio



gen1 gen2 gen3 gen4 gen5 gen6 gen7

Selection of differentially expressed genes

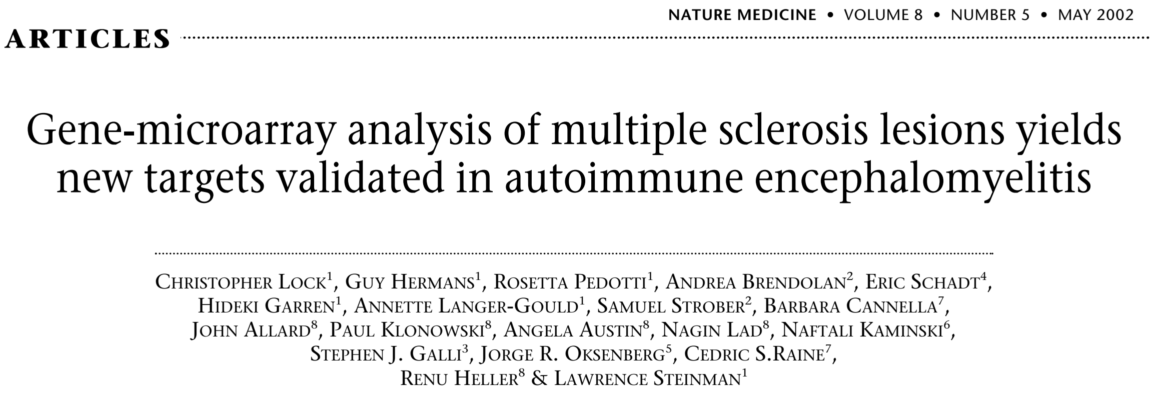
Seed-proteins

Protein-interaction network

1. Ottenimento di dati sperimentali di microarrays e selezione di geni espressi differenzialmente nei pazienti

I risultati sono stati ottenuti dalla letteratura (studi già pubblicati)!

Dati dalla letteratura sui geni upregolati (aumentata espressione) nel tessuto cerebrale nella sclerosi multipla



ARTICLES
NATURE MEDICINE • VOLUME 8 • NUMBER 5 • MAY 2002

Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis

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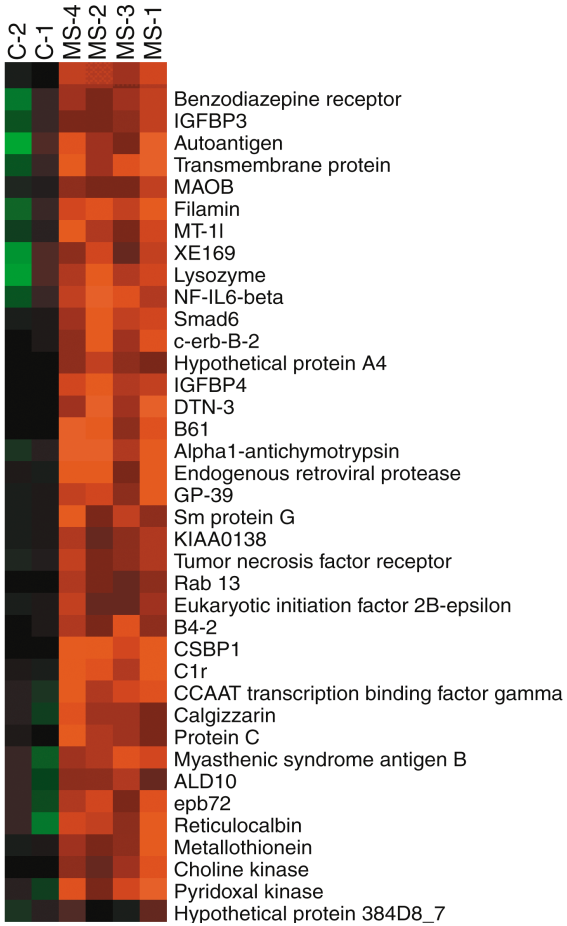

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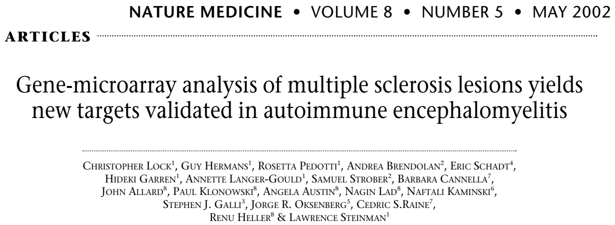

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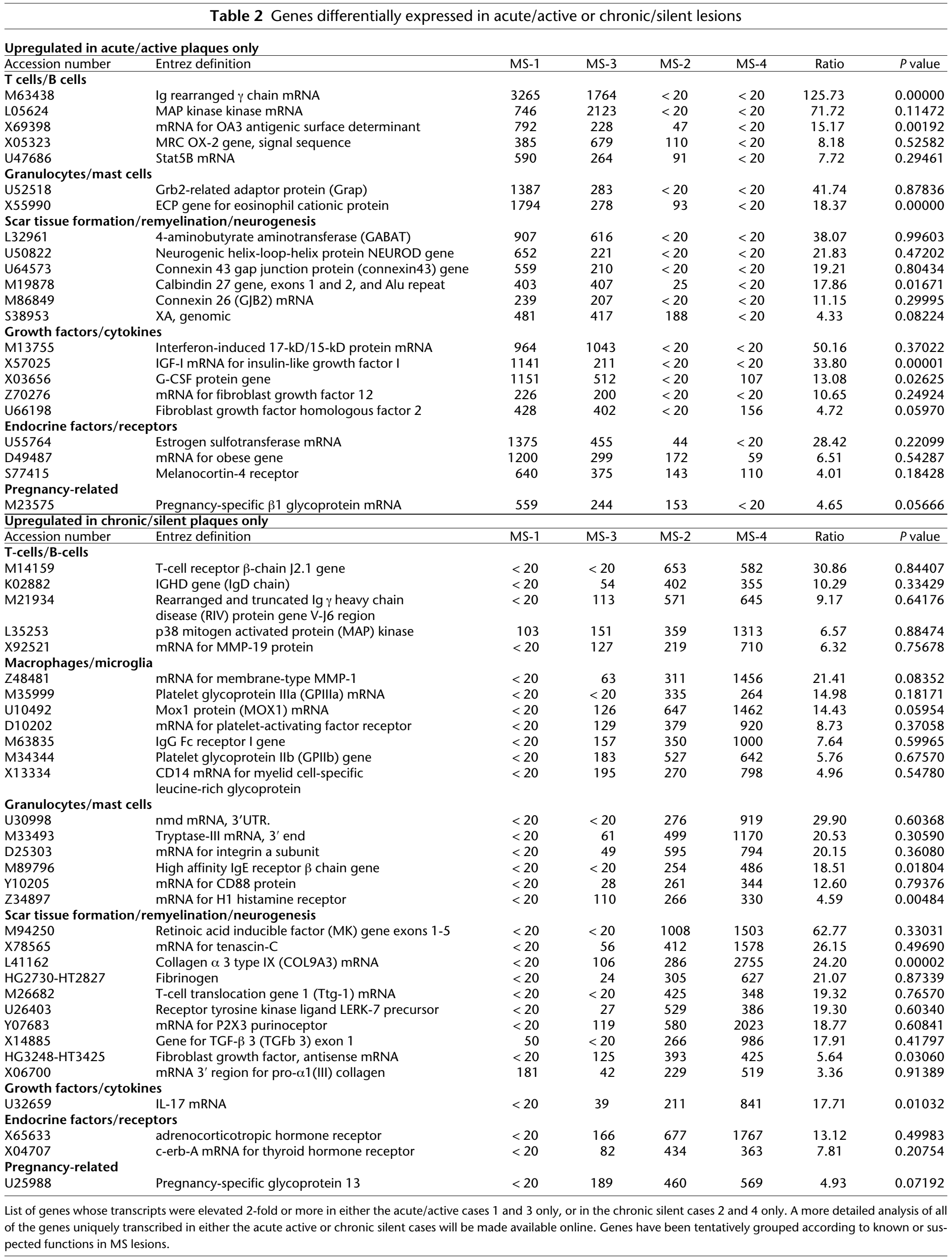

Table 2 Genes differentially expressed in acute/active or chronic/silent lesions

Upregulated in acute/active plaques only

Accession number	Entrez definition	MS-1	MS-3	MS-2	MS-4	Ratio	*P* value
T cells/B cells							
M63438	Ig rearranged γ chain mRNA	3265	1764	< 20	< 20	125.73	0.00000
L05624	MAP kinase kinase mRNA	746	2123	< 20	< 20	71.72	0.11472
X69398	mRNA for OA3 antigenic surface determinant	792	228	47	< 20	15.17	0.00192
X05323	MRC OX-2 gene, signal sequence	385	679	110	< 20	8.18	0.52582
U47686	Stat5B mRNA	590	264	91	< 20	7.72	0.29461
Granulocytes/mast cells							
U52518	Grb2-related adaptor protein (Grap)	1387	283	< 20	< 20	41.74	0.87836
X55990	ECP gene for eosinophil cationic protein	1794	278	93	< 20	18.37	0.00000
Scar tissue formation/remyelination/neurogenesis							
L32961	4-aminobutyrate aminotransferase (GABAT)	907	616	< 20	< 20	38.07	0.99603
U50822	Neurogenic helix-loop-helix protein NEUROD gene	652	221	< 20	< 20	21.83	0.47202
U64573	Connexin 43 gap junction protein (connexin43) gene	559	210	< 20	< 20	19.21	0.80434
M19878	Calbindin 27 gene, exons 1 and 2, and Alu repeat	403	407	25	< 20	17.86	0.01671
M86849	Connexin 26 (GJB2) mRNA	239	207	< 20	< 20	11.15	0.29995
S38953	XA, genomic	481	417	188	< 20	4.33	0.08224
Growth factors/cytokines							
M13755	Interferon-induced 17-kD/15-kD protein mRNA	964	1043	< 20	< 20	50.16	0.37022
X57025	IGF-I mRNA for insulin-like growth factor I	1141	211	< 20	< 20	33.80	0.00001
X03656	G-CSF protein gene	1151	512	< 20	107	13.08	0.02625
Z70276	mRNA for fibroblast growth factor 12	226	200	< 20	< 20	10.65	0.24924
U66198	Fibroblast growth factor homologous factor 2	428	402	< 20	156	4.72	0.05970
Endocrine factors/receptors							
U55764	Estrogen sulfotransferase mRNA	1375	455	44	< 20	28.42	0.22099
D49487	mRNA for obese gene	1200	299	172	59	6.51	0.54287
S77415	Melanocortin-4 receptor	640	375	143	110	4.01	0.18428
Pregnancy-related							
M23575	Pregnancy-specific β1 glycoprotein mRNA	559	244	153	< 20	4.65	0.05666

Upregulated in chronic/silent plaques only

Accession number	Entrez definition	MS-1	MS-3	MS-2	MS-4	Ratio	*P* value
T-cells/B-cells							
M14159	T-cell receptor β-chain J2.1 gene	< 20	< 20	653	582	30.86	0.84407
K02882	IGHD gene (IgD chain)	< 20	54	402	355	10.29	0.33429
M21934	Rearranged and truncated Ig γ heavy chain disease (RIV) protein gene V-J6 region	< 20	113	571	645	9.17	0.64176
L35253	p38 mitogen activated protein (MAP) kinase	103	151	359	1313	6.57	0.88474
X92521	mRNA for MMP-19 protein	< 20	127	219	710	6.32	0.75678
Macrophages/microglia							
Z48481	mRNA for membrane-type MMP-1	< 20	63	311	1456	21.41	0.08352
M35999	Platelet glycoprotein IIIa (GPIIIa) mRNA	< 20	< 20	335	264	14.98	0.18171
U10492	Mox1 protein (MOX1) mRNA	< 20	126	647	1462	14.43	0.05954
D10202	mRNA for platelet-activating factor receptor	< 20	129	379	920	8.73	0.37058
M63835	IgG Fc receptor I gene	< 20	157	350	1000	7.64	0.59965
M34344	Platelet glycoprotein IIb (GPIIb) gene	< 20	183	527	642	5.76	0.67570
X13334	CD14 mRNA for myelid cell-specific leucine-rich glycoprotein	< 20	195	270	798	4.96	0.54780
Granulocytes/mast cells							
U30998	nmd mRNA, 3'UTR.	< 20	< 20	276	919	29.90	0.60368
M33493	Tryptase-III mRNA, 3′ end	< 20	61	499	1170	20.53	0.30590
D25303	mRNA for integrin a subunit	< 20	49	595	794	20.15	0.36080
M89796	High affinity IgE receptor β chain gene	< 20	< 20	254	486	18.51	0.01804
Y10205	mRNA for CD88 protein	< 20	28	261	344	12.60	0.79376
Z34897	mRNA for H1 histamine receptor	< 20	110	266	330	4.59	0.00484
Scar tissue formation/remyelination/neurogenesis							
M94250	Retinoic acid inducible factor (MK) gene exons 1-5	< 20	< 20	1008	1503	62.77	0.33031
X78565	mRNA for tenascin-C	< 20	56	412	1578	26.15	0.49690
L41162	Collagen α 3 type IX (COL9A3) mRNA	< 20	106	286	2755	24.20	0.00002
HG2730-HT2827	Fibrinogen	< 20	24	305	627	21.07	0.87339
M26682	T-cell translocation gene 1 (Ttg-1) mRNA	< 20	< 20	425	348	19.32	0.76570
U26403	Receptor tyrosine kinase ligand LERK-7 precursor	< 20	27	529	386	19.30	0.60340
Y07683	mRNA for P2X3 purinoceptor	< 20	119	580	2023	18.77	0.60841
X14885	Gene for TGF-β 3 (TGFb 3) exon 1	50	< 20	266	986	17.91	0.41797
HG3248-HT3425	Fibroblast growth factor, antisense mRNA	< 20	125	393	425	5.64	0.03060
X06700	mRNA 3′ region for pro-α1(III) collagen	181	42	229	519	3.36	0.91389
Growth factors/cytokines							
U32659	IL-17 mRNA	< 20	39	211	841	17.71	0.01032
Endocrine factors/receptors							
X65633	adrenocorticotropic hormone receptor	< 20	166	677	1767	13.12	0.49983
X04707	c-erb-A mRNA for thyroid hormone receptor	< 20	82	434	363	7.81	0.20754
Pregnancy-related							
U25988	Pregnancy-specific glycoprotein 13	< 20	189	460	569	4.93	0.07192

List of genes whose transcripts were elevated 2-fold or more in either the acute/active cases 1 and 3 only, or in the chronic silent cases 2 and 4 only. A more detailed analysis of all of the genes uniquely transcribed in either the acute active or chronic silent cases will be made available online. Genes have been tentatively grouped according to known or suspected functions in MS lesions.

1. Ottenimento di dati sperimentali di microarrays e selezione di geni espressi differenzialmente nei pazienti

Dati dalla letteratura sui geni upregolati (aumentata espressione) nel sangue in pazienti con sclerosi multipla

Human Molecular Genetics, 2003, Vol. 12, No. 17
DOI: 10.1093/hmg/ddg221

Gene expression profile in multiple sclerosis patients and healthy controls: identifying pathways relevant to disease

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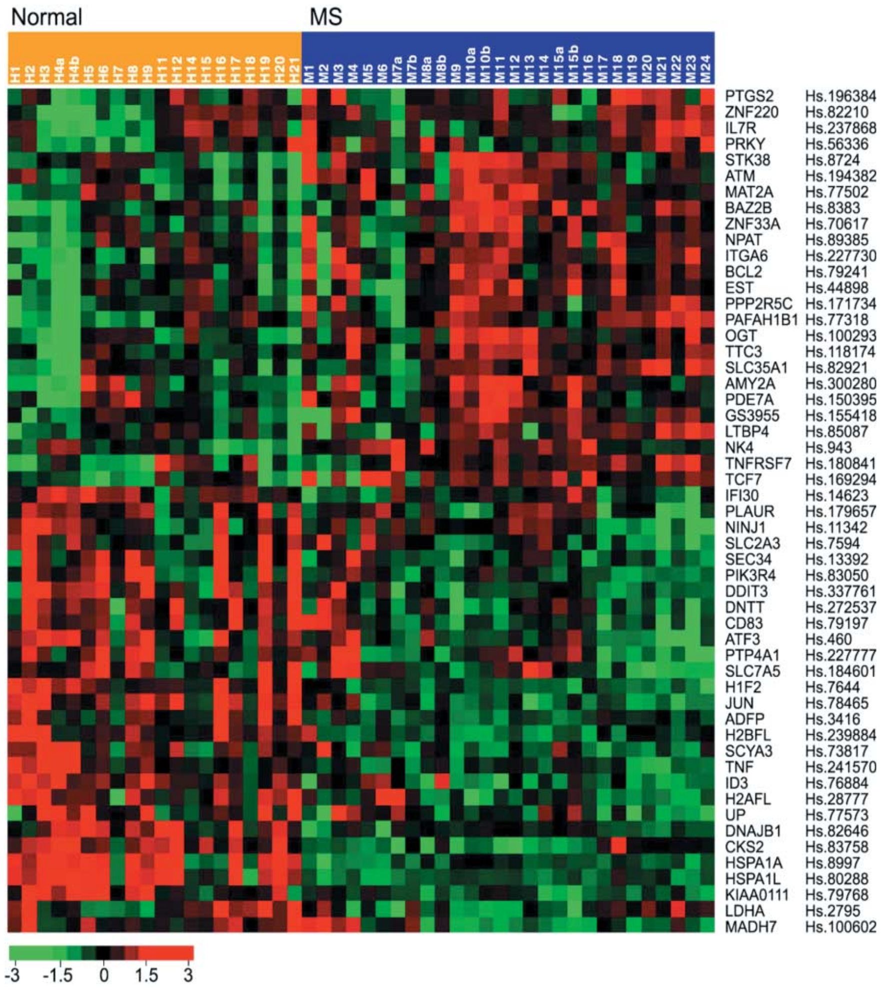

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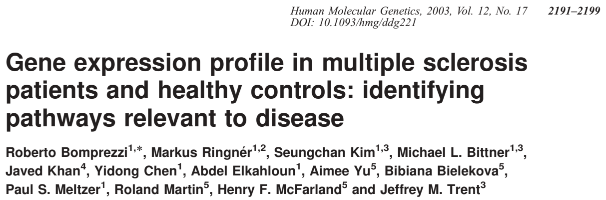

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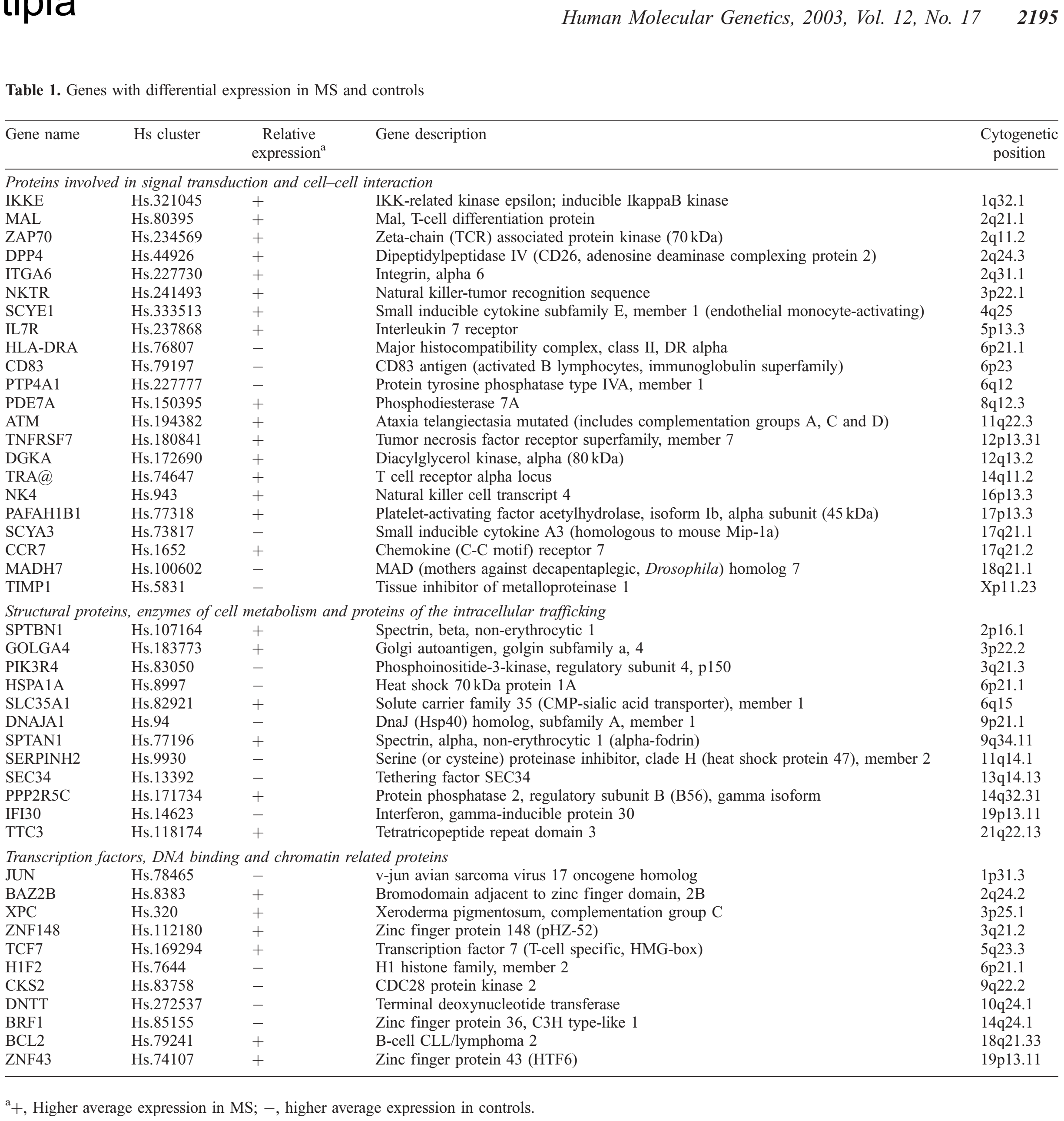


Human Molecular Genetics, 2003, Vol. 12, No. 17 **2195**

Table 1. Genes with differential expression in MS and controls

Gene name	Hs cluster	Relative expression[a]	Gene description	Cytogenetic position
Proteins involved in signal transduction and cell–cell interaction				
IKKE	Hs.321045	+	IKK-related kinase epsilon; inducible IkappaB kinase	1q32.1
MAL	Hs.80395	+	Mal, T-cell differentiation protein	2q21.1
ZAP70	Hs.234569	+	Zeta-chain (TCR) associated protein kinase (70 kDa)	2q11.2
DPP4	Hs.44926	+	Dipeptidylpeptidase IV (CD26, adenosine deaminase complexing protein 2)	2q24.3
ITGA6	Hs.227730	+	Integrin, alpha 6	2q31.1
NKTR	Hs.241493	+	Natural killer-tumor recognition sequence	3p22.1
SCYE1	Hs.333513	+	Small inducible cytokine subfamily E, member 1 (endothelial monocyte-activating)	4q25
IL7R	Hs.237868	+	Interleukin 7 receptor	5p13.3
HLA-DRA	Hs.76807	−	Major histocompatibility complex, class II, DR alpha	6p21.1
CD83	Hs.79197	−	CD83 antigen (activated B lymphocytes, immunoglobulin superfamily)	6p23
PTP4A1	Hs.227777	−	Protein tyrosine phosphatase type IVA, member 1	6q12
PDE7A	Hs.150395	+	Phosphodiesterase 7A	8q12.3
ATM	Hs.194382	+	Ataxia telangiectasia mutated (includes complementation groups A, C and D)	11q22.3
TNFRSF7	Hs.180841	+	Tumor necrosis factor receptor superfamily, member 7	12p13.31
DGKA	Hs.172690	+	Diacylglycerol kinase, alpha (80 kDa)	12q13.2
TRA@	Hs.74647	+	T cell receptor alpha locus	14q11.2
NK4	Hs.943	+	Natural killer cell transcript 4	16p13.3
PAFAH1B1	Hs.77318	+	Platelet-activating factor acetylhydrolase, isoform Ib, alpha subunit (45 kDa)	17p13.3
SCYA3	Hs.73817	−	Small inducible cytokine A3 (homologous to mouse Mip-1a)	17q21.1
CCR7	Hs.1652	+	Chemokine (C-C motif) receptor 7	17q21.2
MADH7	Hs.100602	−	MAD (mothers against decapentaplegic, *Drosophila*) homolog 7	18q21.1
TIMP1	Hs.5831	−	Tissue inhibitor of metalloproteinase 1	Xp11.23
Structural proteins, enzymes of cell metabolism and proteins of the intracellular trafficking				
SPTBN1	Hs.107164	+	Spectrin, beta, non-erythrocytic 1	2p16.1
GOLGA4	Hs.183773	+	Golgi autoantigen, golgin subfamily a, 4	3p22.2
PIK3R4	Hs.83050	−	Phosphoinositide-3-kinase, regulatory subunit 4, p150	3q21.3
HSPA1A	Hs.8997	−	Heat shock 70 kDa protein 1A	6p21.1
SLC35A1	Hs.82921	+	Solute carrier family 35 (CMP-sialic acid transporter), member 1	6q15
DNAJA1	Hs.94	−	DnaJ (Hsp40) homolog, subfamily A, member 1	9p21.1
SPTAN1	Hs.77196	+	Spectrin, alpha, non-erythrocytic 1 (alpha-fodrin)	9q34.11
SERPINH2	Hs.9930	−	Serine (or cysteine) proteinase inhibitor, clade H (heat shock protein 47), member 2	11q14.1
SEC34	Hs.13392	−	Tethering factor SEC34	13q14.13
PPP2R5C	Hs.171734	+	Protein phosphatase 2, regulatory subunit B (B56), gamma isoform	14q32.31
IFI30	Hs.14623	−	Interferon, gamma-inducible protein 30	19p13.11
TTC3	Hs.118174	+	Tetratricopeptide repeat domain 3	21q22.13
Transcription factors, DNA binding and chromatin related proteins				
JUN	Hs.78465	−	v-jun avian sarcoma virus 17 oncogene homolog	1p31.3
BAZ2B	Hs.8383	+	Bromodomain adjacent to zinc finger domain, 2B	2q24.2
XPC	Hs.320	+	Xeroderma pigmentosum, complementation group C	3p25.1
ZNF148	Hs.112180	+	Zinc finger protein 148 (pHZ-52)	3q21.2
TCF7	Hs.169294	+	Transcription factor 7 (T-cell specific, HMG-box)	5q23.3
H1F2	Hs.7644	−	H1 histone family, member 2	6p21.1
CKS2	Hs.83758	−	CDC28 protein kinase 2	9q22.2
DNTT	Hs.272537	−	Terminal deoxynucleotide transferase	10q24.1
BRF1	Hs.85155	−	Zinc finger protein 36, C3H type-like 1	14q24.1
BCL2	Hs.79241	+	B-cell CLL/lymphoma 2	18q21.33
ZNF43	Hs.74107	+	Zinc finger protein 43 (HTF6)	19p13.11

[a] +, Higher average expression in MS; −, higher average expression in controls.

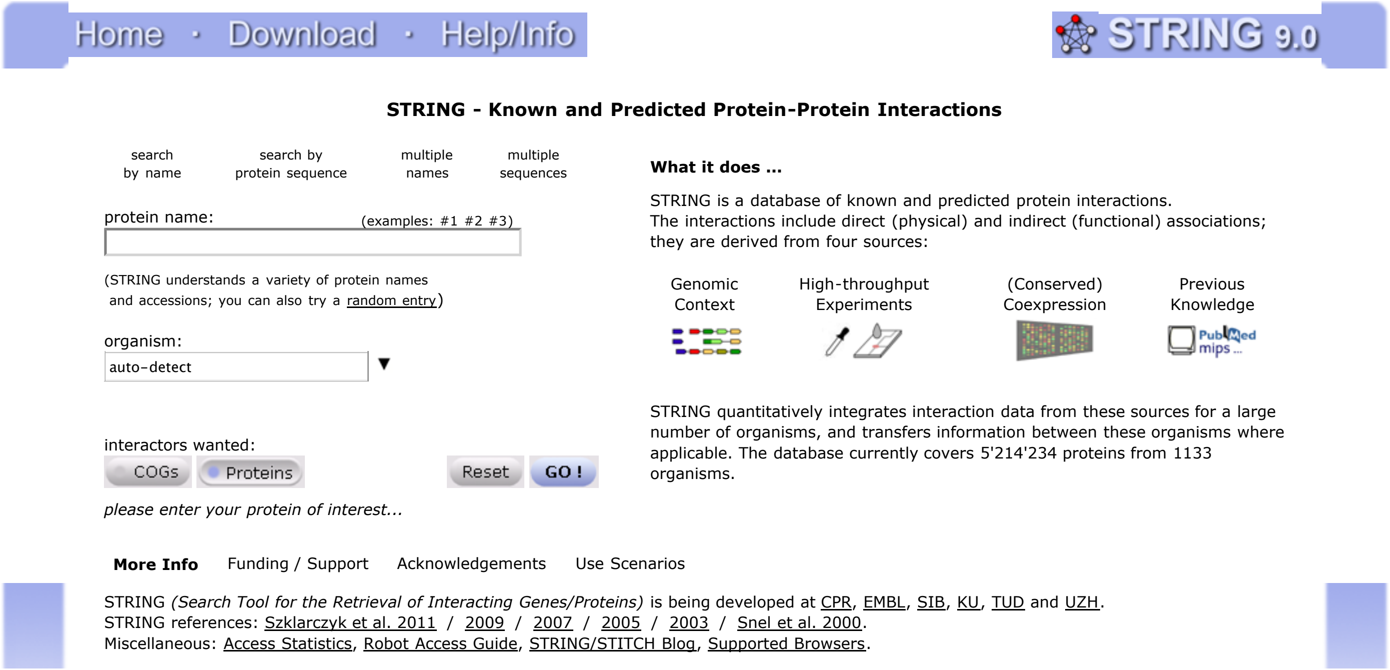
2. Costruzione di network di interazioni proteina-proteina

Costruire il network delle interazioni tra le proteine codificate dai geni identificati al punto 1 e i loro neighbors

Abbiamo bisogno di un database per le PPIs e di un software!

Le informazioni su PPI sono state prese dal String database

http://string-db.org/



STRING - Known and Predicted Protein-Protein Interactions

protein name:

(STRING understands a variety of protein names and accessions; you can also try a random entry)

organism: auto-detect

interactors wanted: ○ COGs ● Proteins

please enter your protein of interest...

What it does ...

STRING is a database of known and predicted protein interactions.
The interactions include direct (physical) and indirect (functional) associations; they are derived from four sources:

STRING quantitatively integrates interaction data from these sources for a large number of organisms, and transfers information between these organisms where applicable. The database currently covers 5'214'234 proteins from 1133 organisms.

STRING *(Search Tool for the Retrieval of Interacting Genes/Proteins)* is being developed at CPR, EMBL, SIB, KU, TUD and UZH.
STRING references: Szklarczyk et al. 2011 / 2009 / 2007 / 2005 / 2003 / Snel et al. 2000.
Miscellaneous: Access Statistics, Robot Access Guide, STRING/STITCH Blog, Supported Browsers.

2. Costruzione di network di interazioni proteina-proteina

Il software utilizzato per la costruzione delle reti: Pajek software

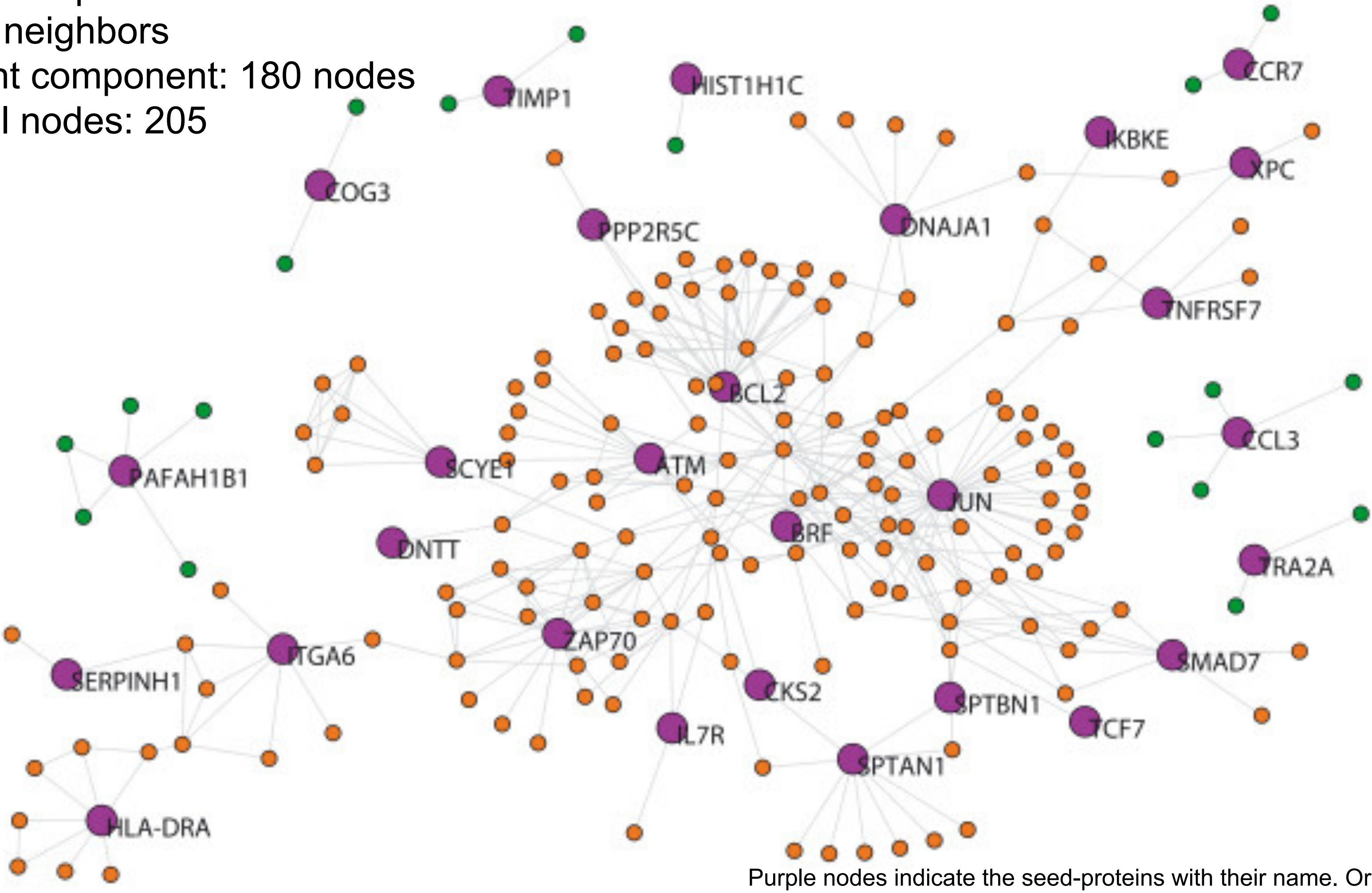
http://pajek.imfm.si/doku.php?id=pajek

2. Costruzione di network di interazioni proteina-proteina

La rete sclerosi multipla - sangue

Meso-scale network

28 seed proteins
177 neighbors
Giant component: 180 nodes
Total nodes: 205

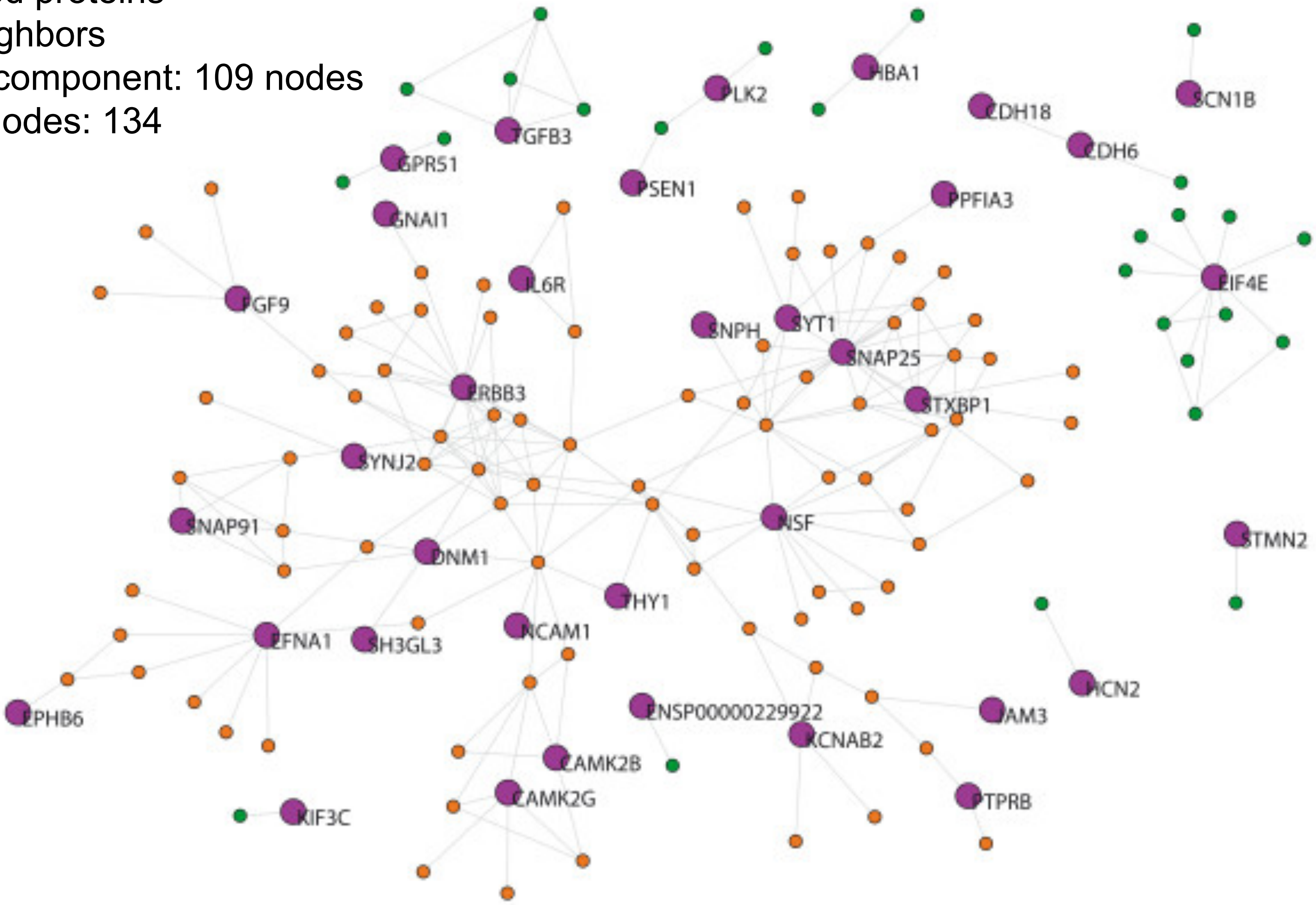


Purple nodes indicate the seed-proteins with their name. Orange nodes indicate neighboring proteins belonging to the giant component. Green nodes indicate neighbors that do not belong to the giant component.

2. Costruzione di network di interazioni proteina-proteina

La rete sclerosi multipla - cervello

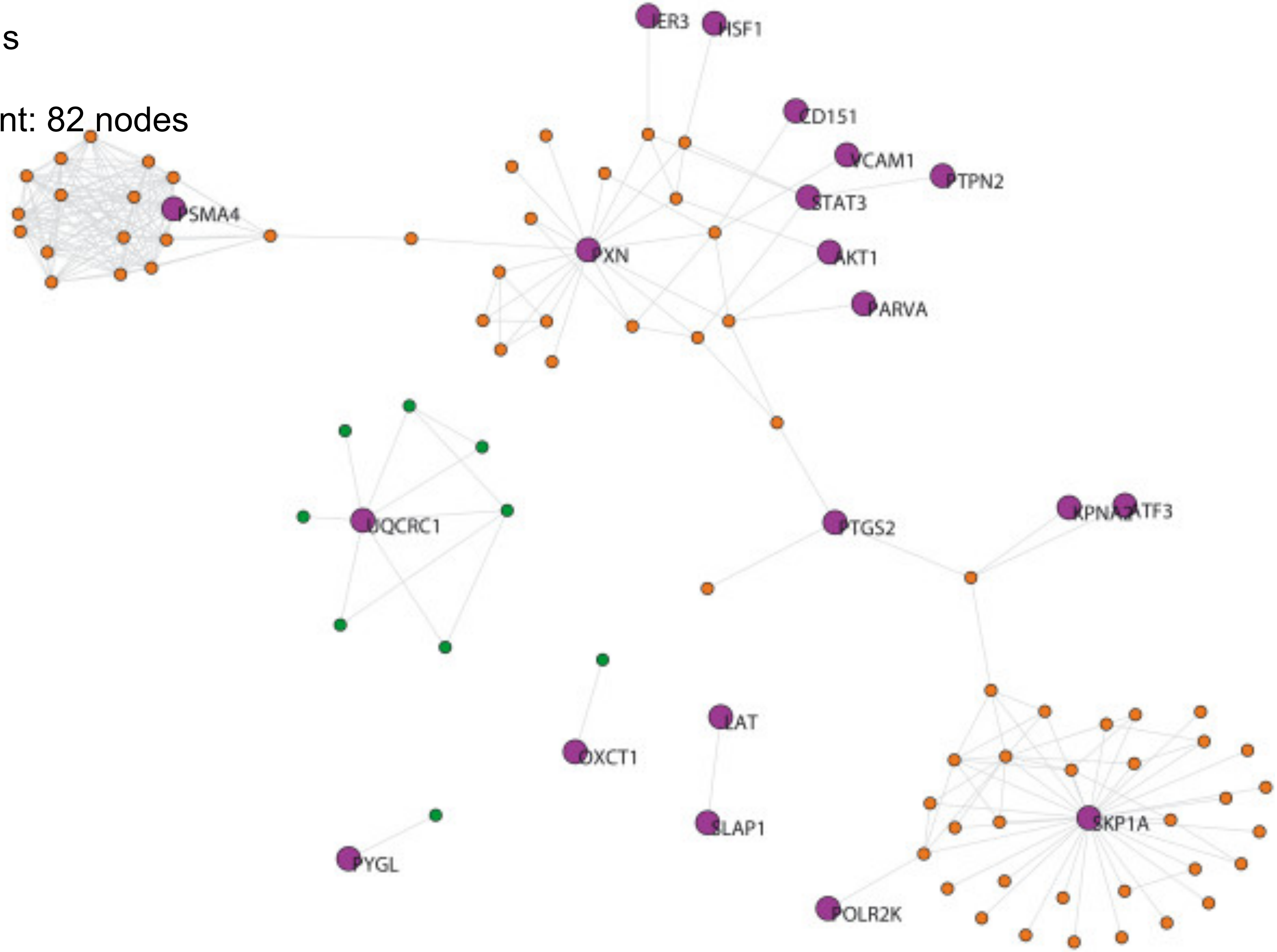
38 seed proteins
96 neighbors
Giant component: 109 nodes
Total nodes: 134



2. Costruzione di network di interazioni proteina-proteina

La rete Alzheimer - sangue

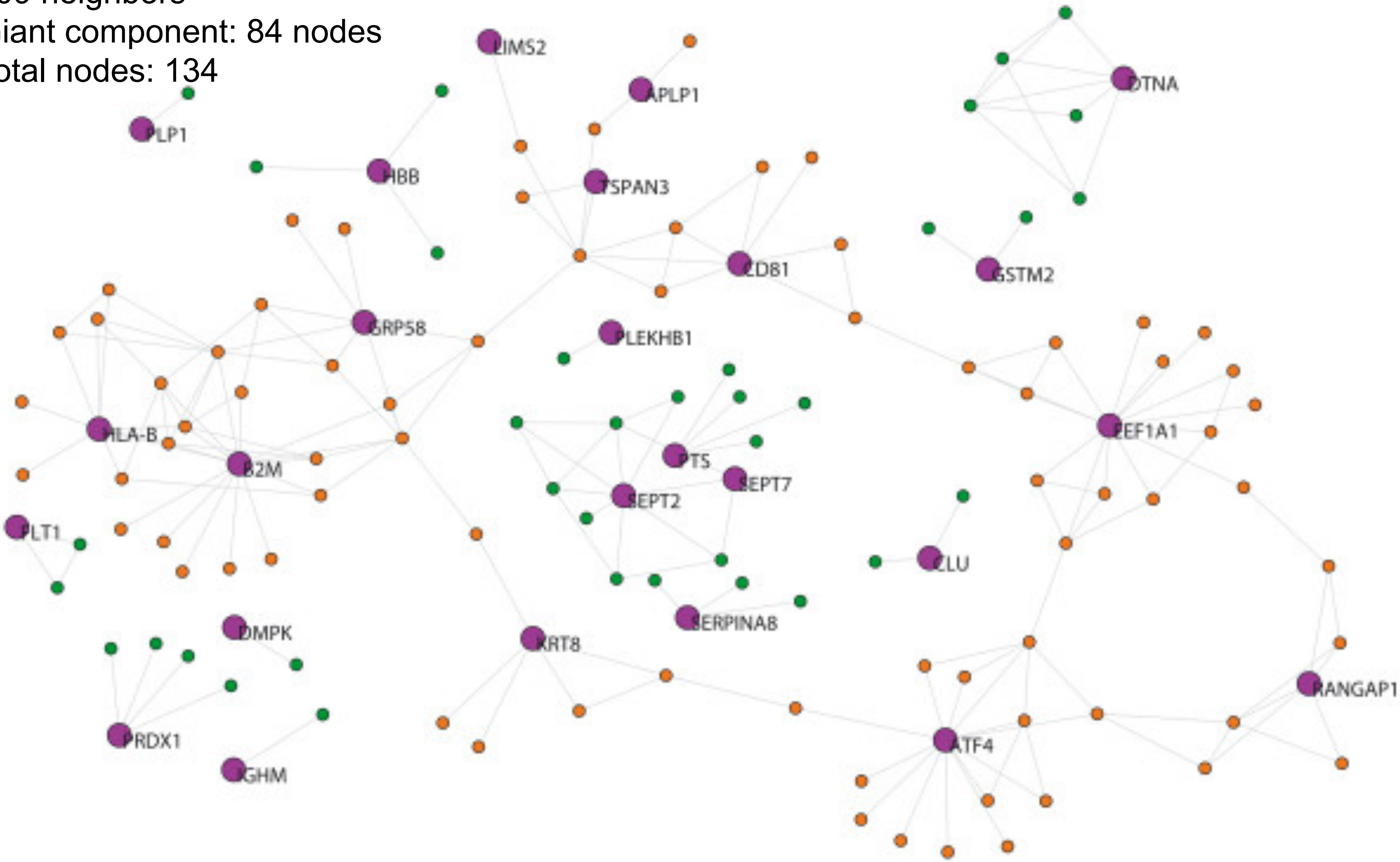
20 seed proteins
76 neighbors
Giant component: 82 nodes
Total nodes: 96



2. Costruzione di network di interazioni proteina-proteina

La rete Alzheimer -cervello

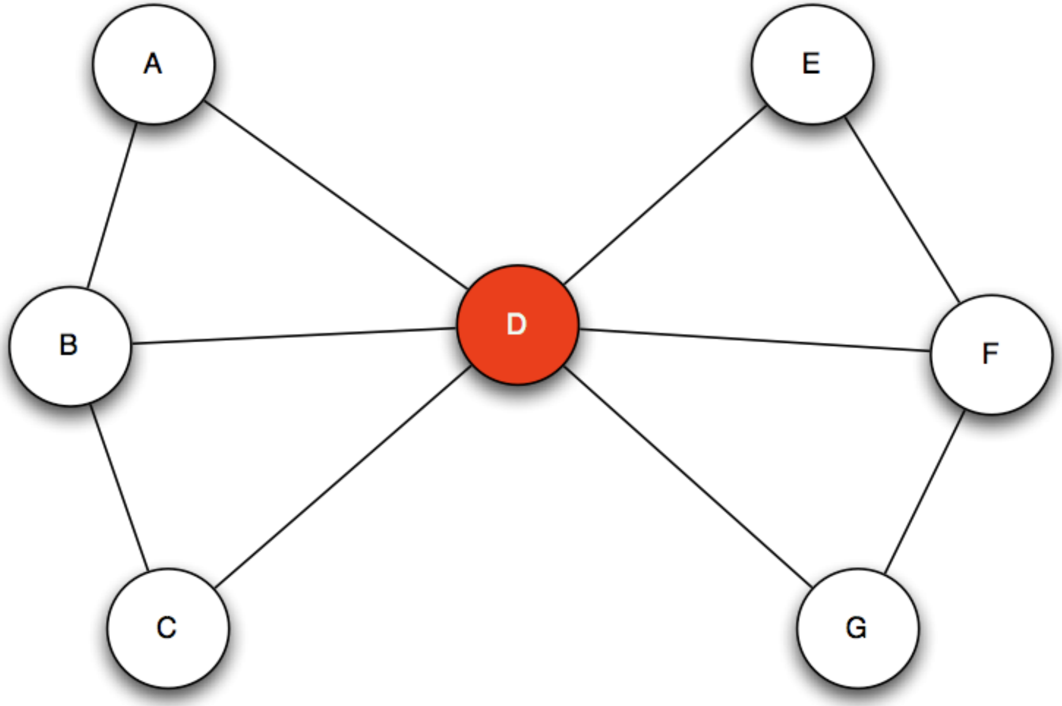
25 seed proteins
109 neighbors
Giant component: 84 nodes
Total nodes: 134



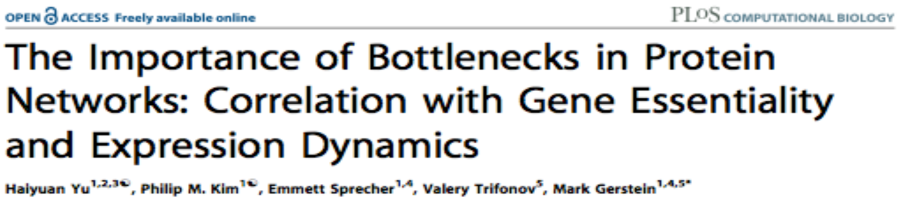
Betweeness centrality

= nodo capace di mettere in comunicazione nodi o zone distinte della rete stessa. Un valore alto di betweenness indica la capacità del nodo di funzionare come nodo comunicatore o “collo di bottiglia” (“bottleneck”).

I nodi bottleneck sono attraversati da tante "shortest paths”; sono come ponti o tunnel in una rete di autostrade



I bottlenecks sono importanti perché sono hubs o per l'alta betweeness?



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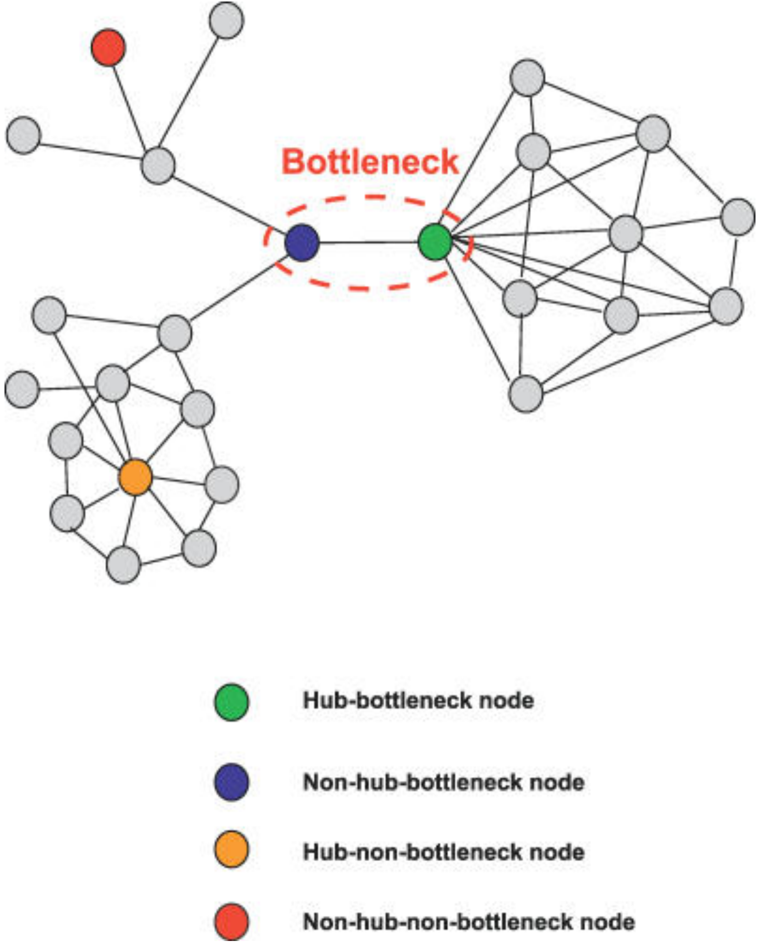
PLoS COMPUTATIONAL BIOLOGY

The Importance of Bottlenecks in Protein Networks: Correlation with Gene Essentiality and Expression Dynamics

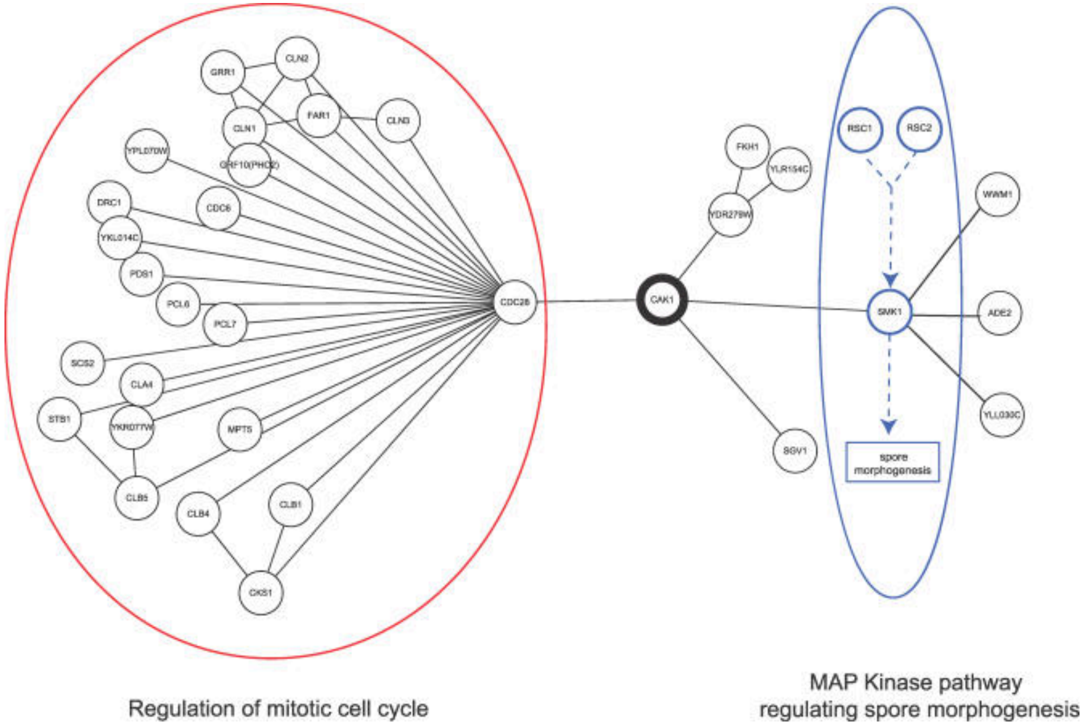
Haiyuan Yu[1,2,3☯], Philip M. Kim[1☯], Emmett Sprecher[1,4], Valery Trifonov[5], Mark Gerstein[1,4,5*]

2007

Tipi di nodi "bottleneck"



Cyclin-dependent kinase bottleneck



La posizione topologica di Cak1 (cyclin-dependent kinase-activating kinase) rende questa molecola (e il suo gene) essenziale per la cellula!

Betweeness centrality

Nelle reti in biologia la betweeness (bottleneck-ness) è un indicatore più significativo di essenzialità rispetto al degree (hubness).

The Gene Ontology project is a major bioinformatics initiative with the aim of standardizing the representation of gene and gene product **attributes** across species and databases. The project provides a controlled vocabulary of terms for describing gene product characteristics and gene product annotation data from GO Consortium members, as well as tools to access and process this data.

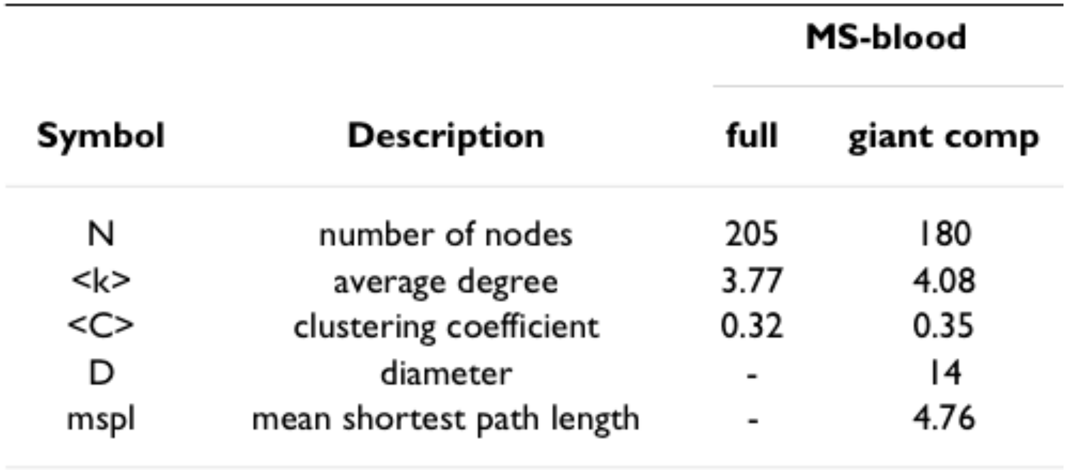
The GO project has developed three structured controlled vocabularies (ontologies) that describe gene products in terms of their associated: 1) **biological processes**, 2) **cellular components** and 3) **molecular functions** in a species-independent manner.

http://www.geneontology.org/

3. Analisi dei networks

La rete sclerosi multipla - sangue

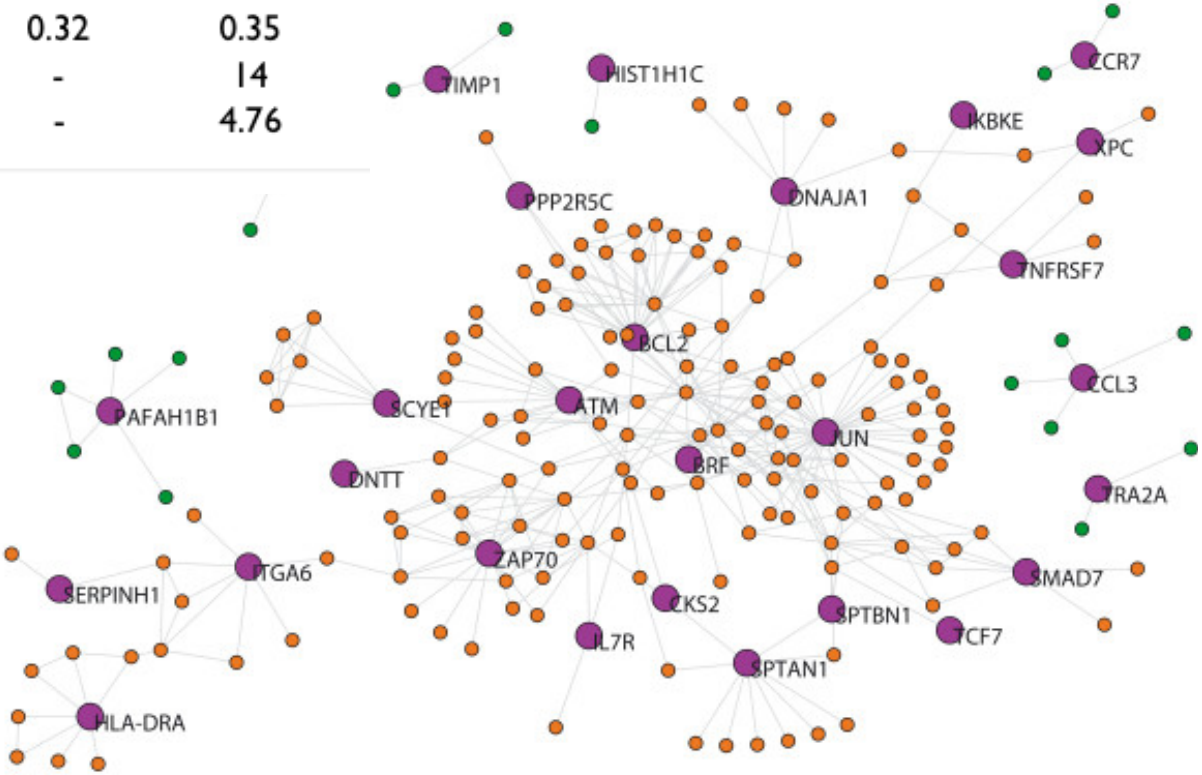
28 seed proteins (su 42 totali)
177 neighbors
Giant component: 180 nodes
Total nodes: 205



Symbol	Description	MS-blood full	MS-blood giant comp
N	number of nodes	205	180
<k>	average degree	3.77	4.08
<C>	clustering coefficient	0.32	0.35
D	diameter	-	14
mspl	mean shortest path length	-	4.76

Le proteine seed hanno il <k> minore rispetto ai nodi neighbors (P<0.05)

36 GO terms sono stati sovraespressi per le proteine seed: risposta immune, migrazione dei leucociti, processi metabolici, risposta allo stress, degradazione proteica



3. Analisi dei networks

La rete sclerosi multipla - sangue

GO Identifier	Gene symbol	GO Term	Over(+)/under(-) representa	p-value	FDR
GO:0006955	BCL2, CCL3, CCR7, CD27, CD8	immune response	+	1,55E-06	0,0008122
GO:0000003	ATM, BCL2, CCL3, CCR7, CD27	reproduction	+	2,53E-05	0,0066286
GO:0009408	BCL2, DNAJA1, SERPINH1	response to heat	+	0,0001948	0,0340251
GO:0007182	SMAD7, SPTBN1	common-partner SMAD protein phosphorylation	+	0,000262	0,0343259
GO:0045069	BCL2, CCL3	regulation of viral genome replication	+	0,0004521	0,0358648
GO:0050900	CCL3, ITGA6, SCYE1	leukocyte migration	+	0,0005185	0,0358648
GO:0050794	ATM, BAZ2B, BCL2, BRF1, CD2	regulation of cellular process	+	0,0005231	0,0358648
GO:0016485	ATM, JUN, PPP2R5C, ZAP70	protein processing	+	0,0006289	0,0358648
GO:0016032	BCL2, CCL3, CCR7	viral reproduction	+	0,0006742	0,0358648
GO:0007165	ATM, BCL2, CCL3, CCR7, CD27	signal transduction	+	0,0006844	0,0358648
GO:0007276	ATM, CD27, DNAJA1, PAFAH1B	gametogenesis	+	0,0008919	0,0380501
GO:0050896	ATM, BCL2, CCL3, CCR7, CD27	response to stimulus	+	0,0009169	0,0380501
GO:0009892	JUN, SLC12A8, SMAD7, SPTAN	negative regulation of metabolic process	+	0,0010097	0,0380501
GO:0045582	CD27, ZAP70	positive regulation of T cell differentiation	+	0,0010892	0,0380501
GO:0050792	BCL2, CCL3	regulation of viral life cycle	+	0,0010892	0,0380501
GO:0046777	ATM, JUN, ZAP70	protein amino acid autophosphorylation	+	0,0013541	0,0411615
GO:0045621	CD27, ZAP70	positive regulation of lymphocyte differentiation	+	0,0014436	0,0411615
GO:0051016	SPTAN1, SPTBN1	barbed-end actin filament capping	+	0,0015724	0,0411615
GO:0051607	BCL2, SCYE1	defense response to virus	+	0,0015724	0,0411615
GO:0016540	ATM, JUN, ZAP70	protein autoprocessing	+	0,0016337	0,0411615
GO:0019953	ATM, CD27, DNAJA1, PAFAH1B	sexual reproduction	+	0,0018148	0,0411615
GO:0051693	SPTAN1, SPTBN1	actin filament capping	+	0,0018458	0,0411615
GO:0030835	SPTAN1, SPTBN1	negative regulation of actin filament depolymeriza	+	0,0019904	0,0411615
GO:0019079	BCL2, CCL3	viral genome replication	+	0,0022951	0,0411615
GO:0006952	BCL2, CCL3, CCR7, CD83, HLA	defense response	+	0,0024409	0,0411615
GO:0032848	BCL2	negative regulation of cellular pH reduction	+	0,0024569	0,0411615
GO:0035026	JUN	leading edge cell differentiation	+	0,0024569	0,0411615
GO:0046730	CCR7	induction of host immune response by virus	+	0,0024569	0,0411615
GO:0051045	TIMP1	negative regulation of membrane protein ectodomain	+	0,0024569	0,0411615
GO:0030042	SPTAN1, SPTBN1	actin filament depolymerization	+	0,0026205	0,0411615
GO:0042981	ATM, BCL2, CD27, MAL, PIK3R	regulation of apoptosis	+	0,002638	0,0411615
GO:0007154	ATM, BCL2, CCL3, CCR7, CD27	cell communication	+	0,0026549	0,0411615
GO:0050793	ATM, BCL2, CD27, MAL, PIK3R	regulation of developmental process	+	0,0027572	0,0411615
GO:0045580	CD27, ZAP70	regulation of T cell differentiation	+	0,0027908	0,0411615
GO:0043067	ATM, BCL2, CD27, MAL, PIK3R	regulation of programmed cell death	+	0,0027937	0,0411615
GO:0044267	ATM, C6orf165, CD27, DNAJA1,	cellular protein metabolic process	+	0,0028279	0,0411615

FDR = false discovery rate correction

3. Analisi dei networks

La rete sclerosi multipla - cervello

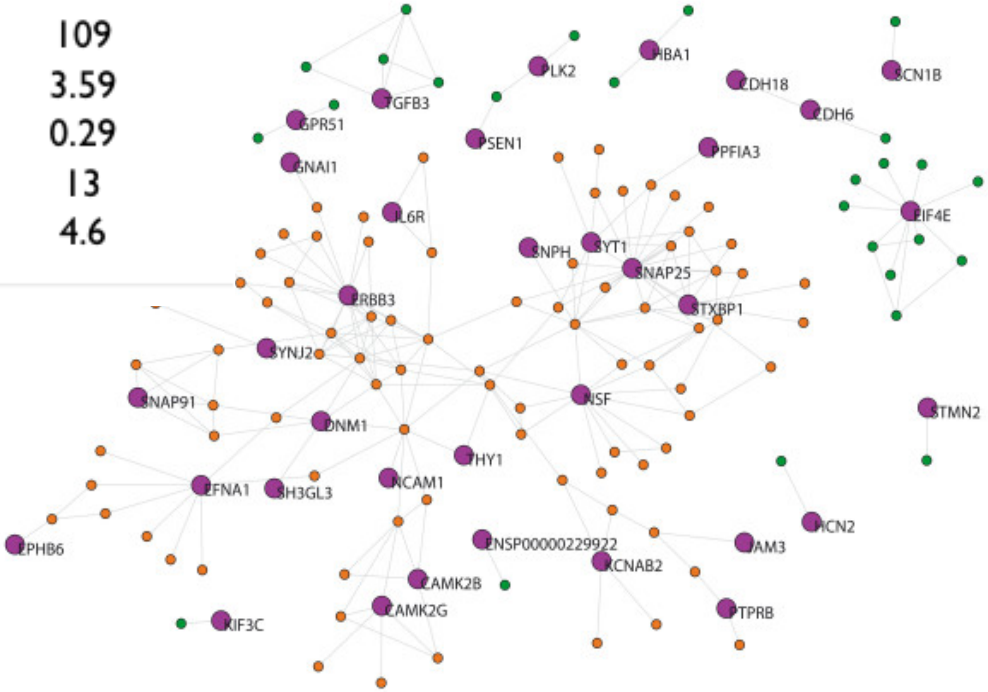
38 seed proteins (su 99 totali)
96 neighbors
Giant component: 109 nodes
Total nodes: 134

		MS-brain	
Symbol	**Description**	**full**	**giant comp**
N	number of nodes	148	109
<k>	average degree	3.12	3.59
<C>	clustering coefficient	0.26	0.29
D	diameter	-	13
mspl	mean shortest path length	-	4.6

Le proteine seed hanno il <k> minore rispetto ai nodi neighbors (P<0.05)

Le proteine seed hanno la betweeness maggiore rispetto ai nodi neighbors (P<0.05)

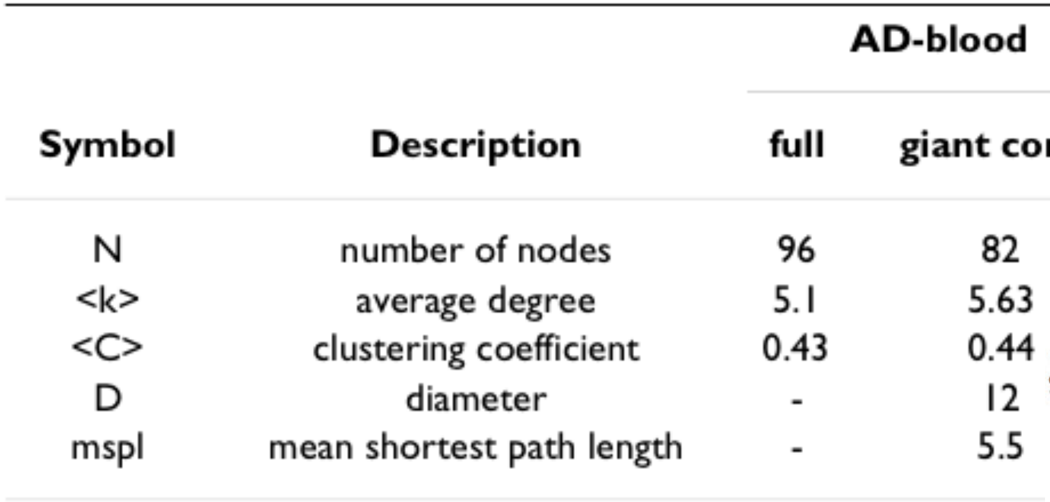
67 GO terms sono stati sovraespressi per le proteine seed: risposta immune, trasmissione sinaptica, neurogenesi, differenziazione neuronale



3. Analisi dei networks

La rete Alzheimer - sangue

20 seed proteins (su 142 totali)
76 neighbors
Giant component: 82 nodes
Total nodes: 96

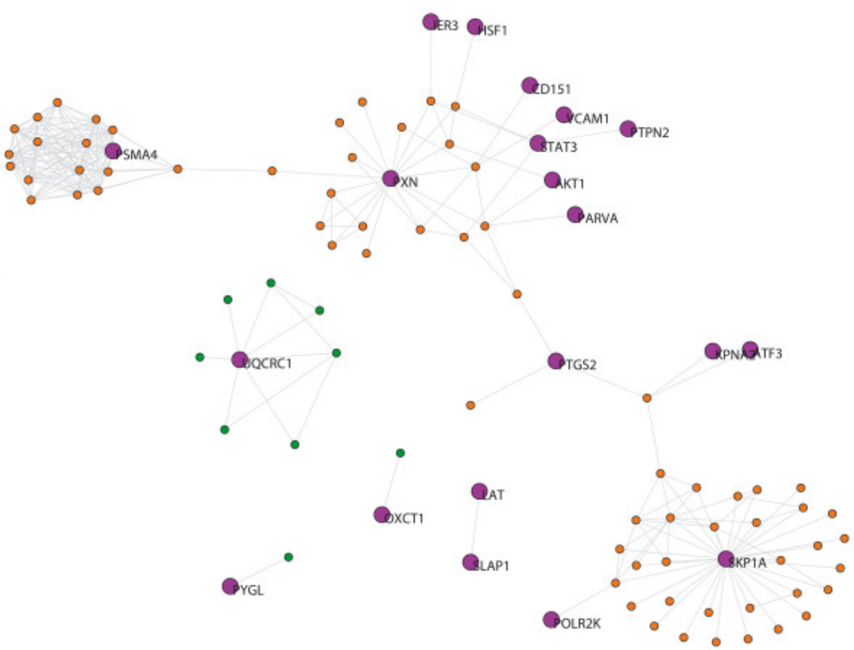


Symbol	Description	AD-blood full	AD-blood giant comp
N	number of nodes	96	82
<k>	average degree	5.1	5.63
<C>	clustering coefficient	0.43	0.44
D	diameter	-	12
mspl	mean shortest path length	-	5.5

Le proteine seed hanno il <k> minore rispetto ai nodi neighbors (P<0.05)

Le proteine seed hanno la betweeness maggiore rispetto ai nodi neighbors (P<0.05)

Nessun GO term è sovraespresso

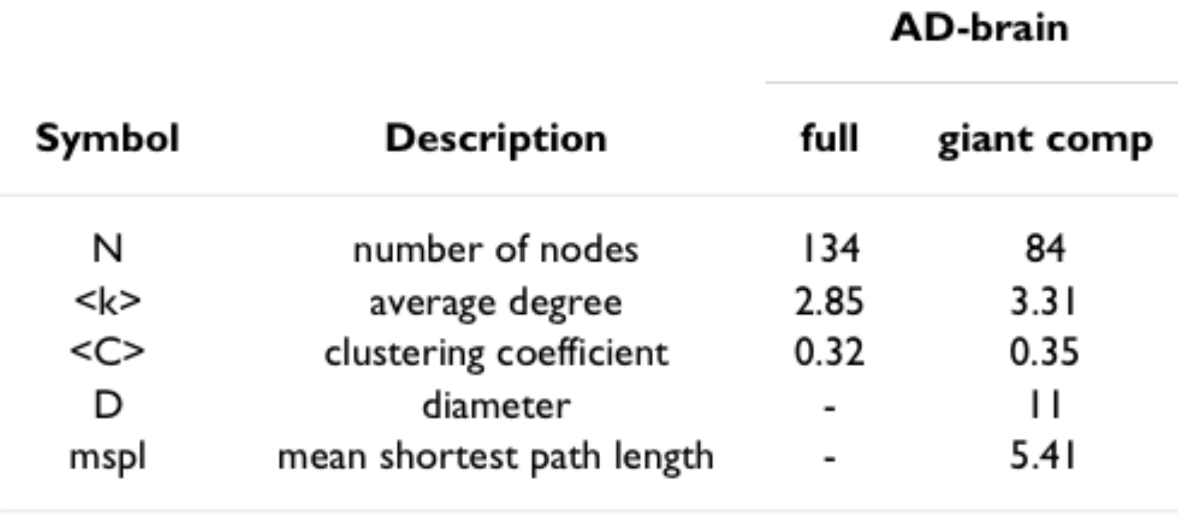


3. Analisi dei networks

La rete Alzheimer -cervello

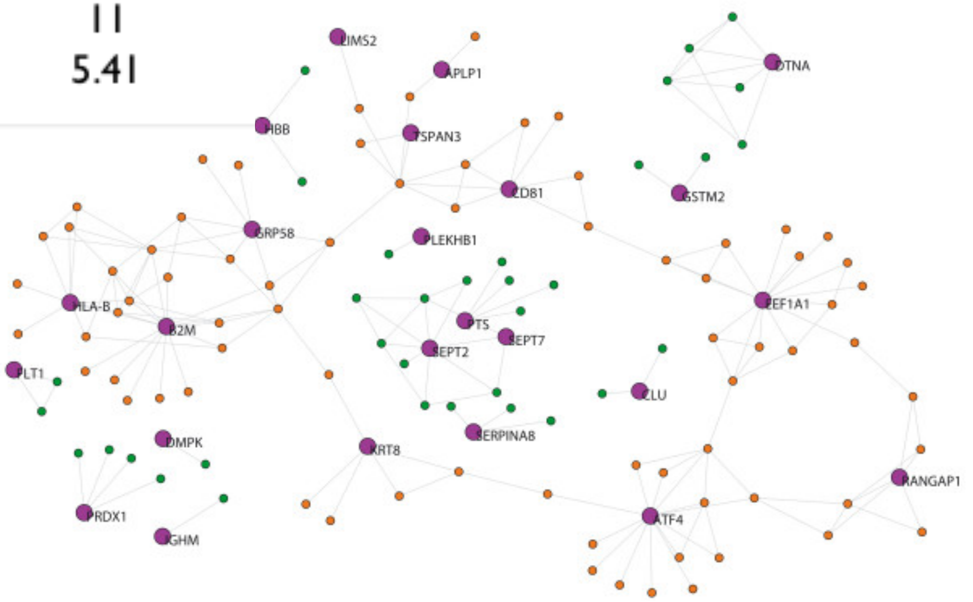
25 seed proteins (su 35 totali
109 neighbors
Giant component: 84 nodes
Total nodes: 134

Le proteine seed hanno il <k> minore rispetto ai nodi neighbors (P<0.05)



		AD-brain	
Symbol	Description	full	giant comp
N	number of nodes	134	84
<k>	average degree	2.85	3.31
<C>	clustering coefficient	0.32	0.35
D	diameter	-	11
mspl	mean shortest path length	-	5.41

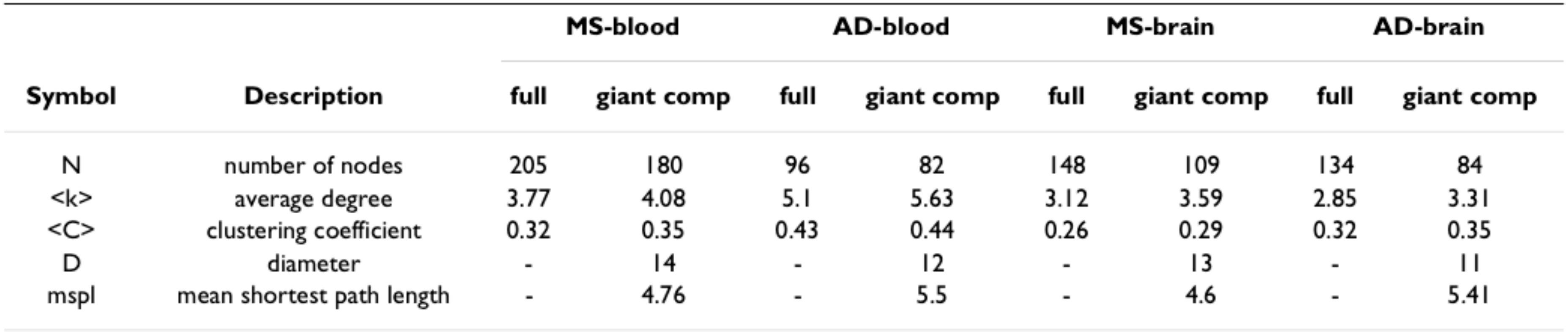
18 GO terms sono stati sovraespressi per le proteine seed: sviluppo del CNS, trasporto dell’ossigeno, contrazione delle fibre muscolari lisce, attivazione del complemento, processazione dell’antigene, risposta umorale



4. Conclusioni:

1. L’applicazione indica un approccio valido per studiare le PPI networks a livello di meso-scala utilizzando i prodotti dei geni espressi differenzialmente nei pazienti rispetto ai soggetti sani

2. Le 4 reti costruite non mostrano differenze significative riguardo i parametri misurati, suggerendo una certa omogenità dello studio



		MS-blood		AD-blood		MS-brain		AD-brain	
Symbol	Description	full	giant comp	full	giant comp	full	giant comp	full	giant comp
N	number of nodes	205	180	96	82	148	109	134	84
<k>	average degree	3.77	4.08	5.1	5.63	3.12	3.59	2.85	3.31
<C>	clustering coefficient	0.32	0.35	0.43	0.44	0.26	0.29	0.32	0.35
D	diameter	-	14	-	12	-	13	-	11
mspl	mean shortest path length	-	4.76	-	5.5	-	4.6	-	5.41

4. Conclusioni:

3. Il degree medio delle proteine seed è basso.

4. I termini GO sono molto vari e riflettono la complessità delle due malattie

5. La hubness delle proteine seed sembra meno importante nelle malattie complesse studiate considerando il degree medio basso in tutte le quattro reti studiate. La betweeness (più alta dei nodi seed in due reti e in due tessutti diversi) sembra un parametro più importante della hubness

6. I nodi con alta betweeness e i nodi poco connessi (anche periferici) potrebbero rappresentare nuovi potenziali bersagli farmacologici nelle malattie complesse (multifattoriali)

Conclusioni

7. Nelle malattie multifattoriali le monoterapie che colpiscono solamente un nodo/pathway della rete dovrebbero essere meno efficaci rispetto a terapie multiple che inibiscono le funzioni di nodi multipli (pathways multiple)

8. Ogni studente che ha una buona idea scientifica potrebbe fare uno studio simile se possiede un computer e ha capito il corso di systems biology!