

## Lecture III

# Multiscale Gene Networks Remodeling in Alzheimer's Disease

**Bin Zhang, PhD**

Department of Genetics & Genomic Sciences  
Icahn Institute of Genomics and Multiscale Biology  
Icahn School of Medicine at Mount Sinai, New York, USA

Email: [bin.zhang@mssm.edu](mailto:bin.zhang@mssm.edu)

Web: <http://research.mssm.edu/multiscalenetwork>

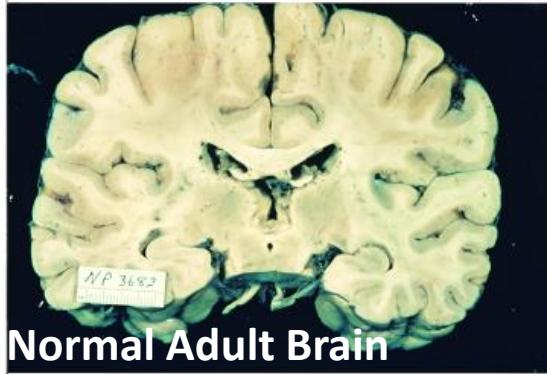


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# Alzheimer's Disease

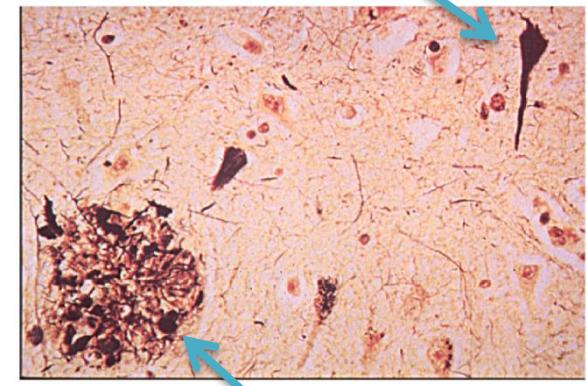
- ❖ Alzheimer's disease (AD) is the most common form of degenerative dementia. AD prevalence is increasing at an alarming rates and is expected to affect over **100 million** cases worldwide in 2050.
- ❖ Hippocampus and surrounding cortical regions are the major sites of AD-related pathology, characterized by increasing accumulation of Ab-amyloid plaques and Tau-related neurofibrillary tangles.
- ❖ Three rare forms of early onset familial AD have been identified and are associated with mutations in APP, PS1 and PS2 genes.
- ❖ The more common late onset form of AD (LOAD) is assumed to be polygenic/multifactorial.
- ❖ So far the only clearly identified genetic risk factor for AD is Apo lipoprotein E (APOE). **The ε4 allele of ApoE influences age at onset of AD, but is neither necessary nor sufficient for the disease.**



Normal Adult Brain



Alzheimer Brain



Neuritic plaques

Neurofibrillary tangles

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August 18, 2010

# Doubt on Tactic in Alzheimer's Battle

By [GINA KOLATA](#)

The failure of a promising [Alzheimer's](#) drug in clinical trials highlights the gap between diagnosis — where real progress has recently been made — and treatment of the disease.

It was not just that the drug, made by Eli Lilly, did not work — maybe that could be explained by saying the patients' illness was too far advanced when they received it. It was that the drug actually made them worse, the company said. And the larger the dose they took, the worse were patients' symptoms of [memory loss](#) and inability to care for themselves. Not only that, the drug also increased the risk of [skin cancer](#).

.....

The Lilly study's failure, he said, "chips away at that approach to testing the amyloid hypothesis."

"We don't know what the drug targets for Alzheimer's disease are," Dr. Schneider said. "We don't know because we don't know the causes of Alzheimer's."

At the very least, said Dr. P. Murali Doraiswamy, an Alzheimer's researcher at Duke University, the Lilly result "clearly tells us that our current views may be too simplistic."

.....

# More AD Drugs Failed !!??

The New York Times

May 7, 2013

## Alzheimer's Treatment Failed Trial, Maker Says

By ANDREW POLLACK

In yet another setback for the treatment of Alzheimer's disease, Baxter International said Tuesday that its drug, Gammagard, had failed to halt the mental decline of patients with mild-to-moderate Alzheimer's.

Prospects that  
had gone th

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Baxter said  
functioning

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## Pfizer Alzheimer's Drug Dimebon Fails in Study



By COURTNEY HUTCHISON

## Lilly drug slows Alzheimer's in some, fails main goals

Fri, Aug 24 2012

By Michele Gershberg and Julie Steenhuysen

NEW YORK/CHICAGO (Reuters) - Eli Lilly and Co said its experimental Alzheimer's drug showed signs of slowing mental decline in patients with a mild form of the disease, even though it failed to meet the main goals of two large clinical trials, suggesting the treatment could be salvaged.

Shares of the company rose as much as 6 percent on Friday as investors bet the treatment, solanezumab, may help patients in the early stages of the disease, which has so far stumped the research efforts of the world's largest drugmakers.

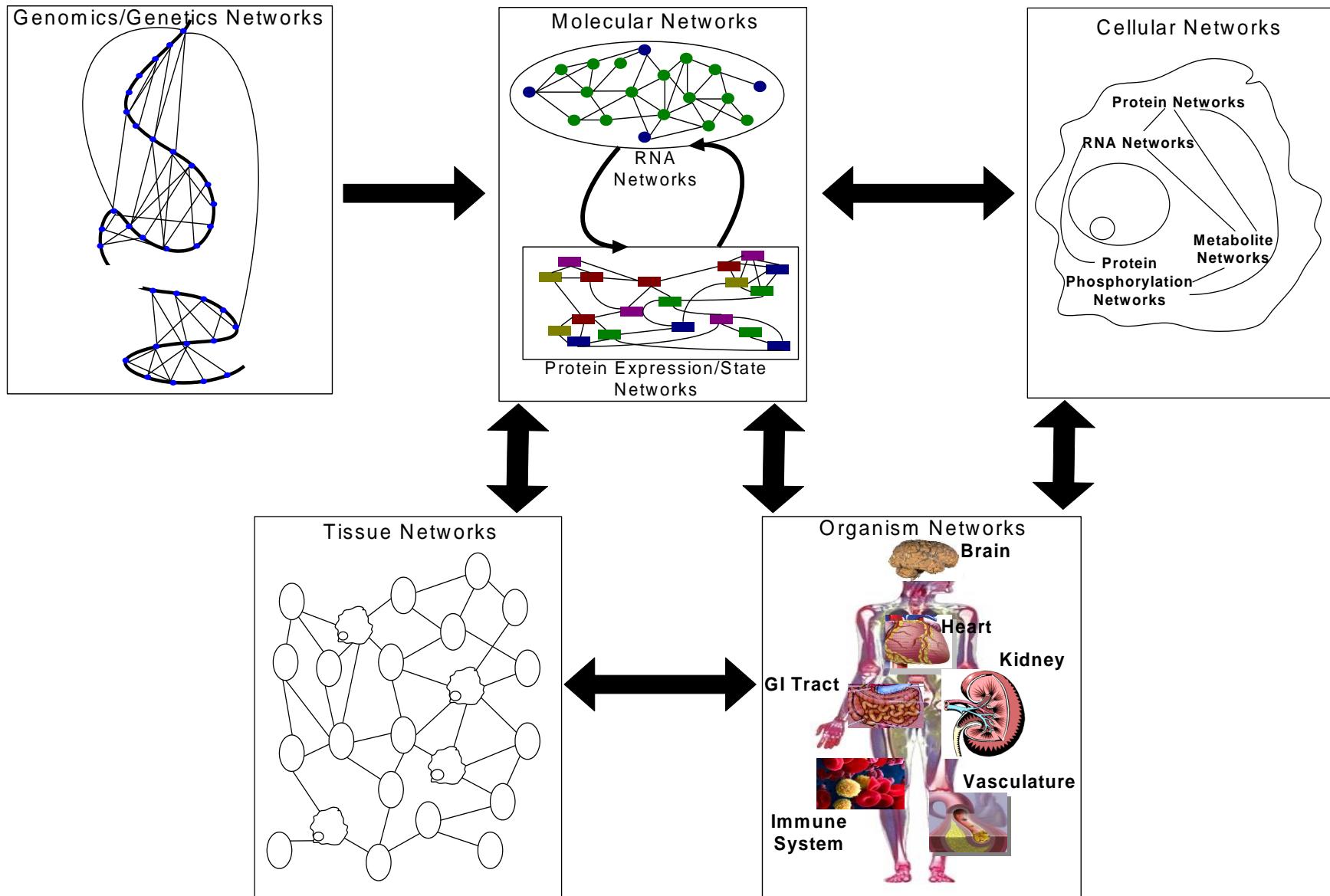
Lilly did not give detailed data on its findings, but its executives said they were the first glimmer of hope in a large clinical trial that removing the toxic protein beta amyloid from the brains of Alzheimer's patients might alter the course of the disease.

Scientists were far more cautious and said it was impossible to gauge what the findings mean until full results are released at a neurology meeting on October 8 in Boston.

The late-stage trials, known as EXPEDITION 1 and 2, tested solanezumab in patients with mild-to-moderate Alzheimer's disease, compared with a placebo. Both of these studies failed to meet their primary goals.

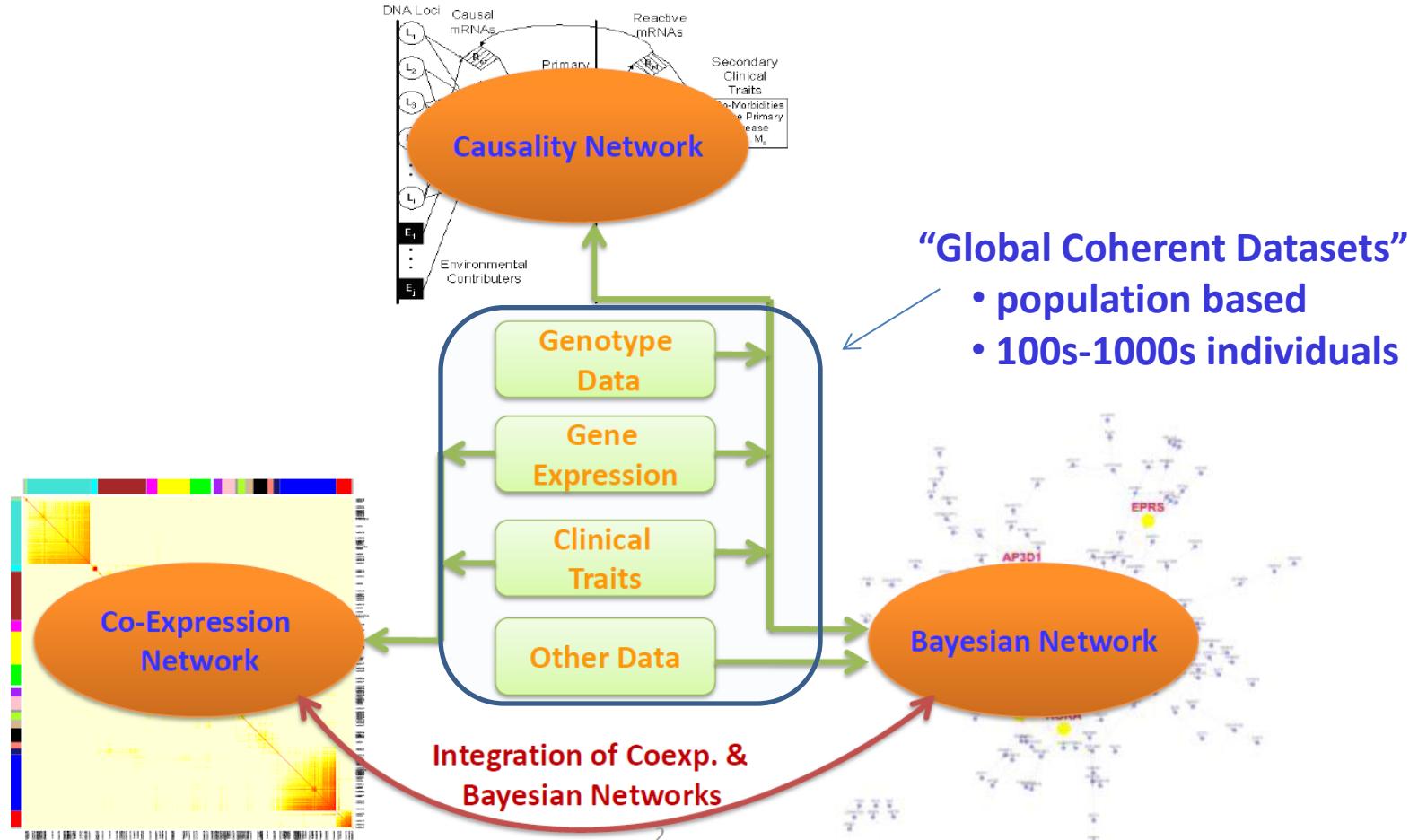


# A Network-centered View of Biological Systems



# Methods for Integration of Genotypic, Gene Expression & Clinical Data

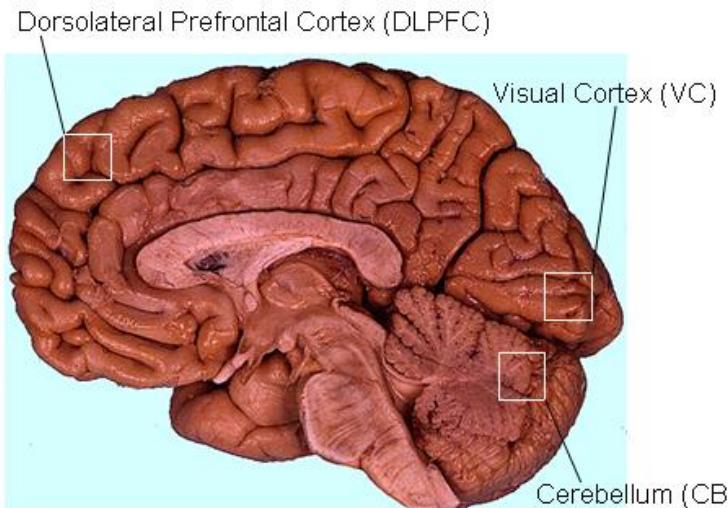
Schadt et al. *Nature Genetics* 37: 710 (2005)  
Millstein, Zhang et al. *BMC Genetics* 10:23 (2009)



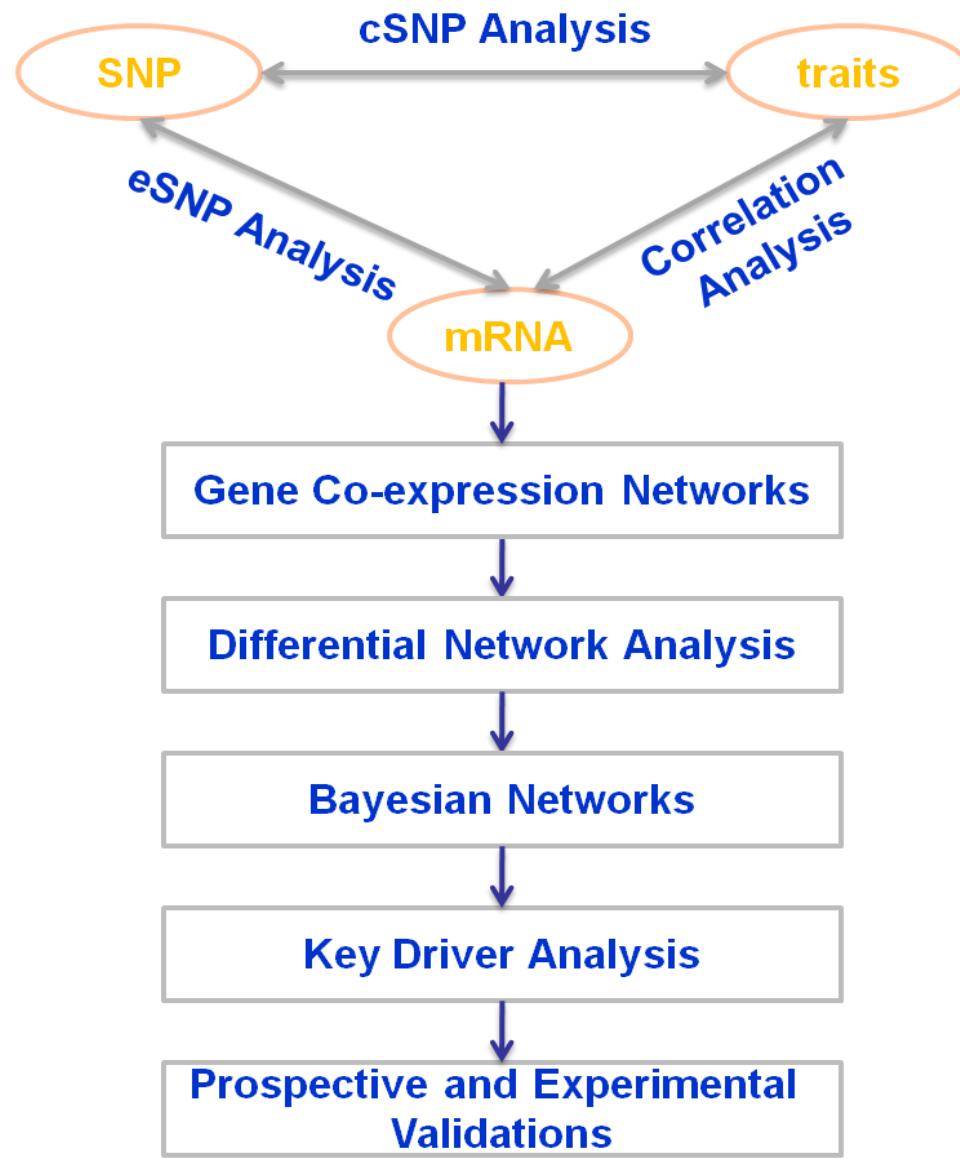
Zhang & Horvath. *Stat.Appl.Genet.Mol.Biol.* 4: article 17 (2005)  
Yang, Zhang et al. *Genome Research* 20:8 (2010)  
Wang, Zhang et al. *Mol Sys Biol* 8:594 (2012)

Zhu et al. *Cytogenet Genome Res.* 105:363 (2004)  
Zhu, Zhang et al. *Nature Genetics* 40: 854-861 (2008)  
Zhu , Sova et al. *PLoS Biology* 10:4 (2012)

# Overview of HBBAD Cohort and Analysis Flow

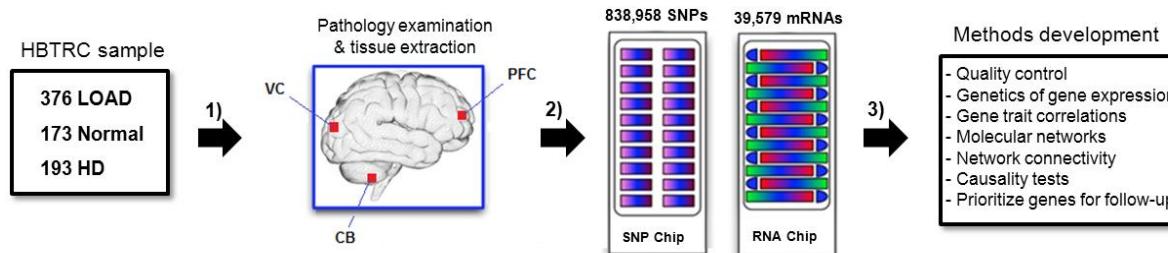


subset	samples
Alzh_PFC	310
Alzh_CR	263
Alzh_VC	190
Norm_PFC	153
Norm_CR	128
Norm_VC	121

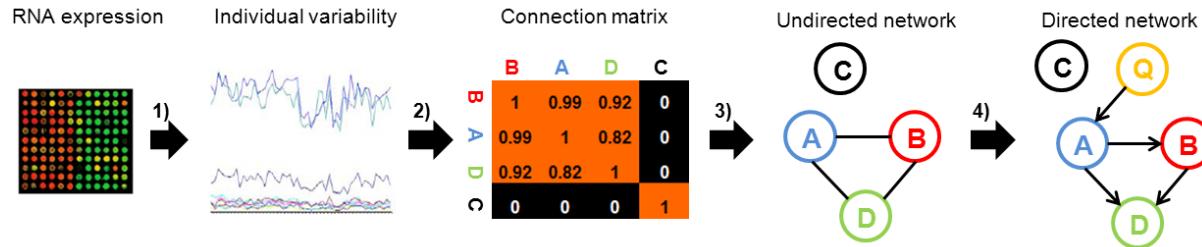


# Sample Processing and Multiscale Network Analysis

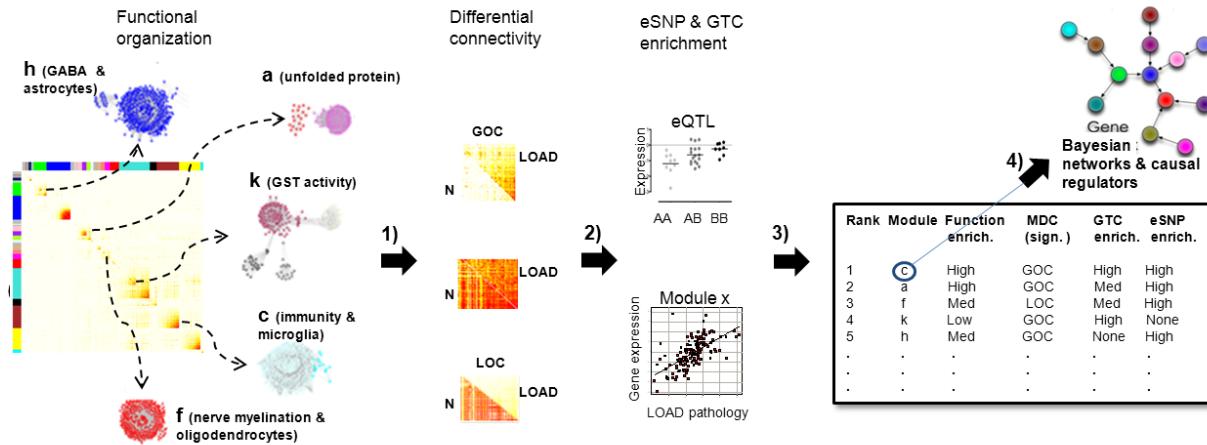
## Sample Preparation & Profiling



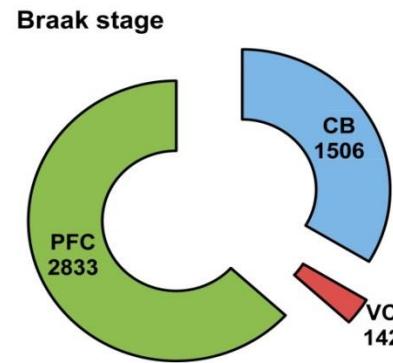
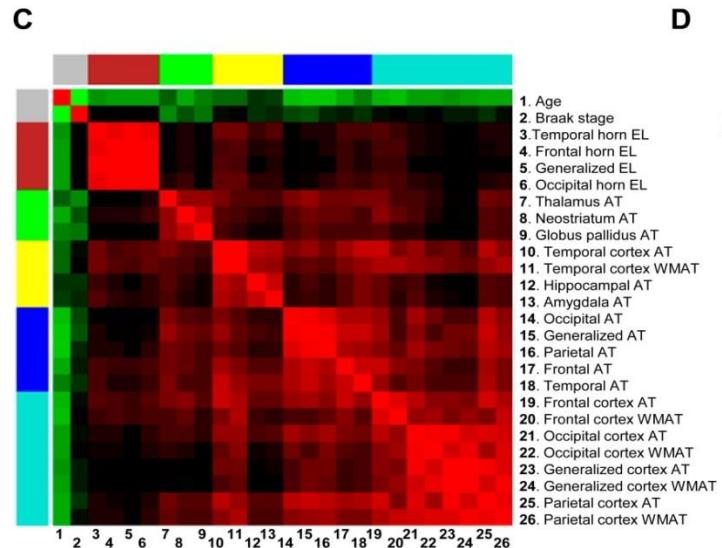
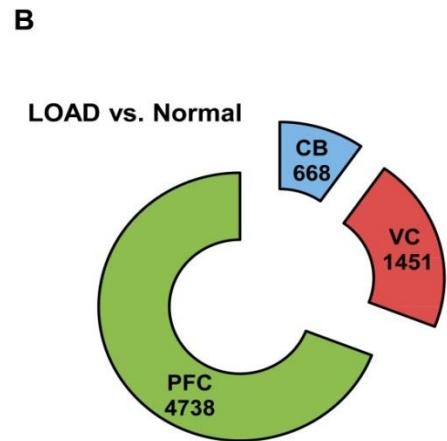
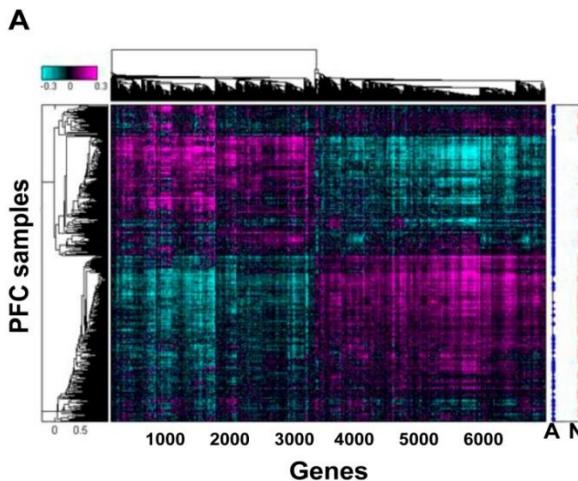
## Network Construction



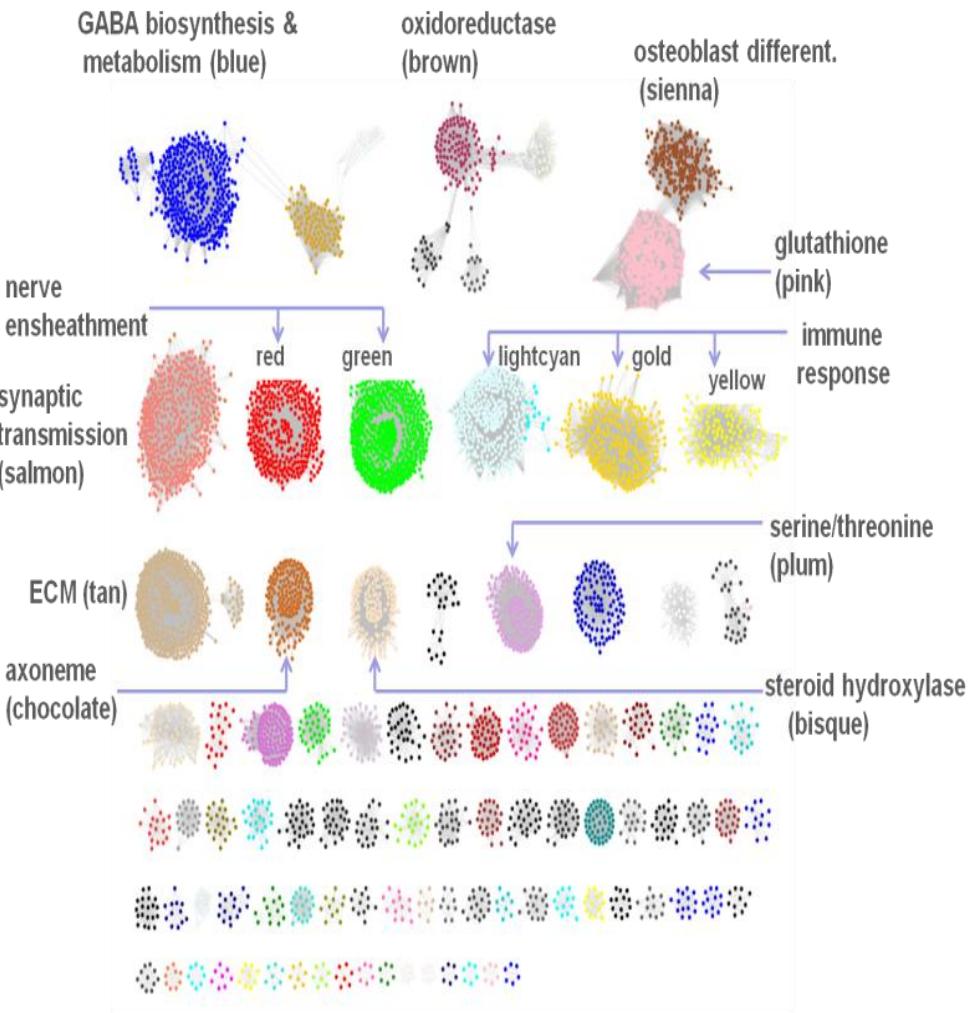
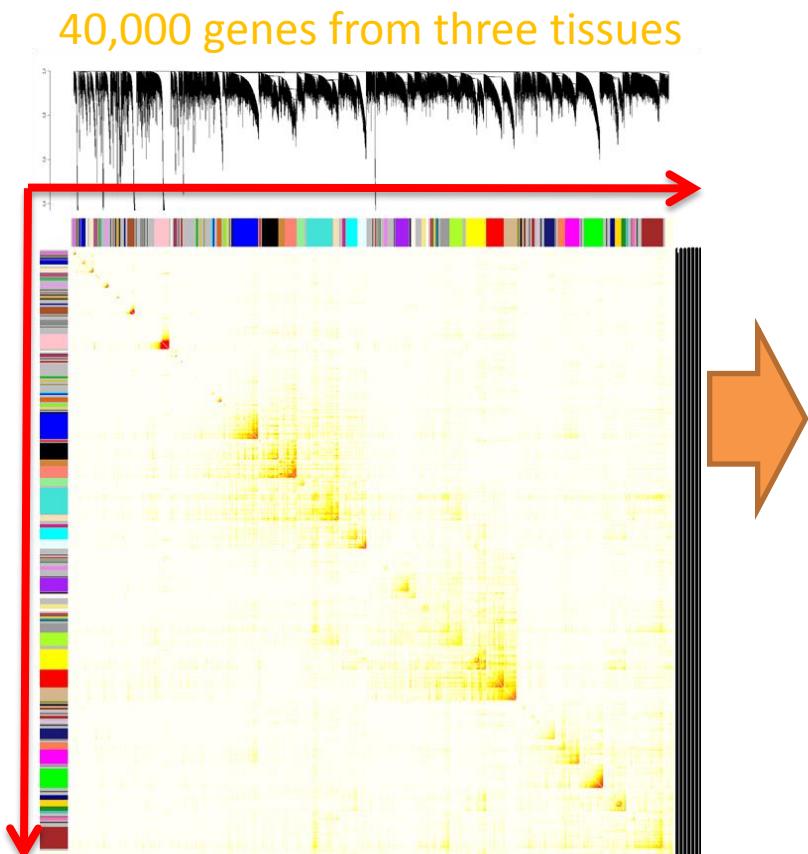
## Network Analysis



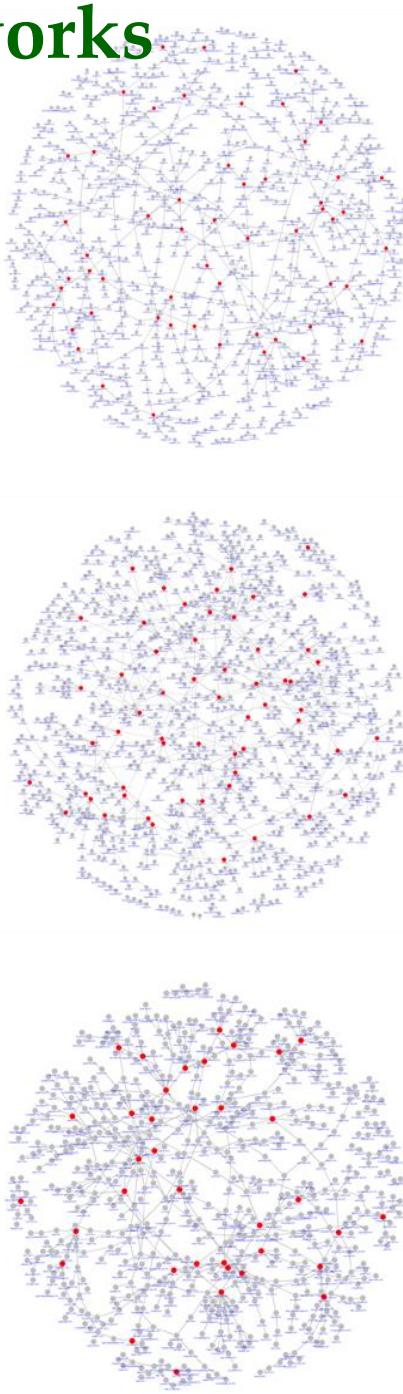
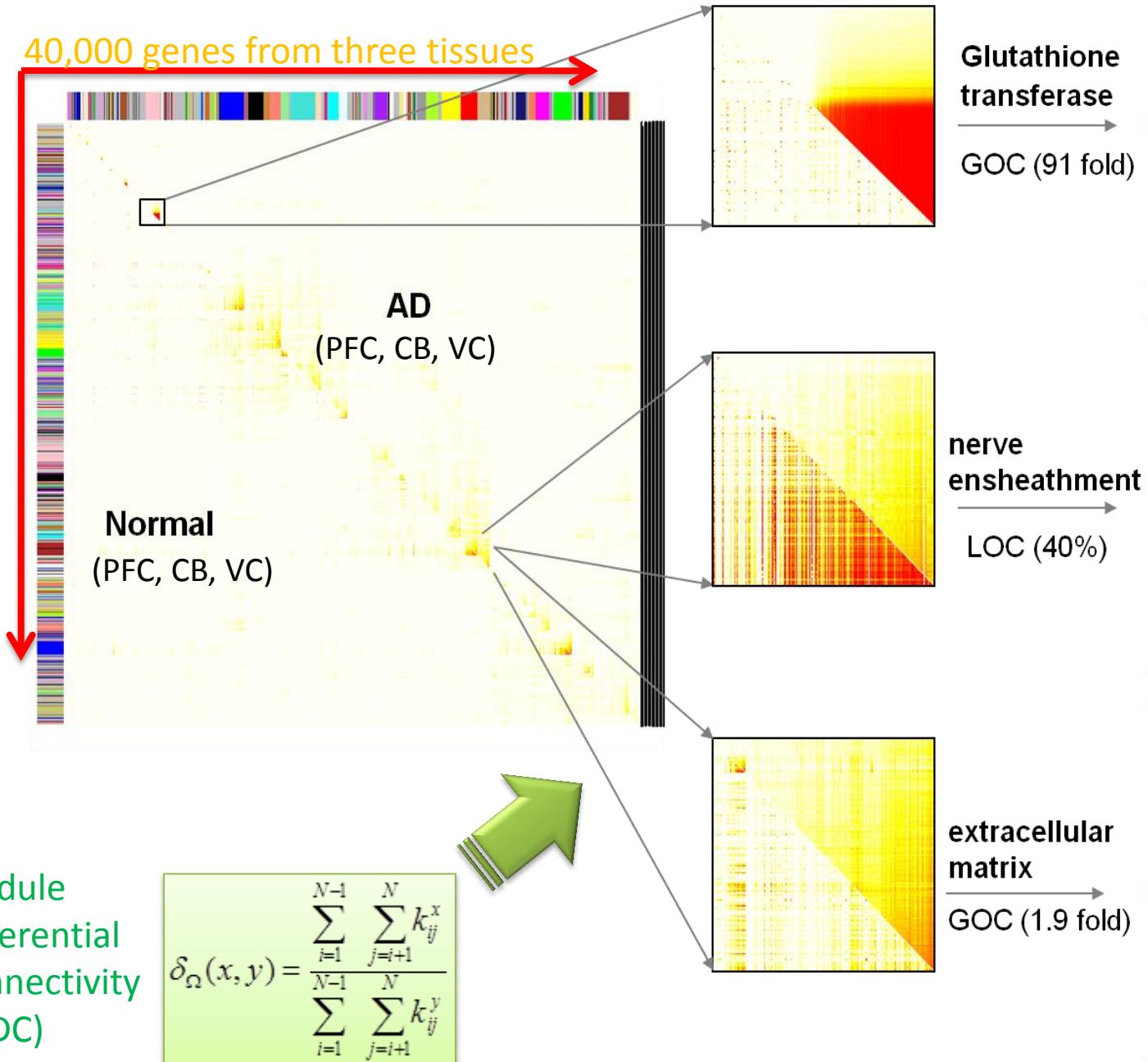
# Differential Gene Expression and Gene-Trait Correlation



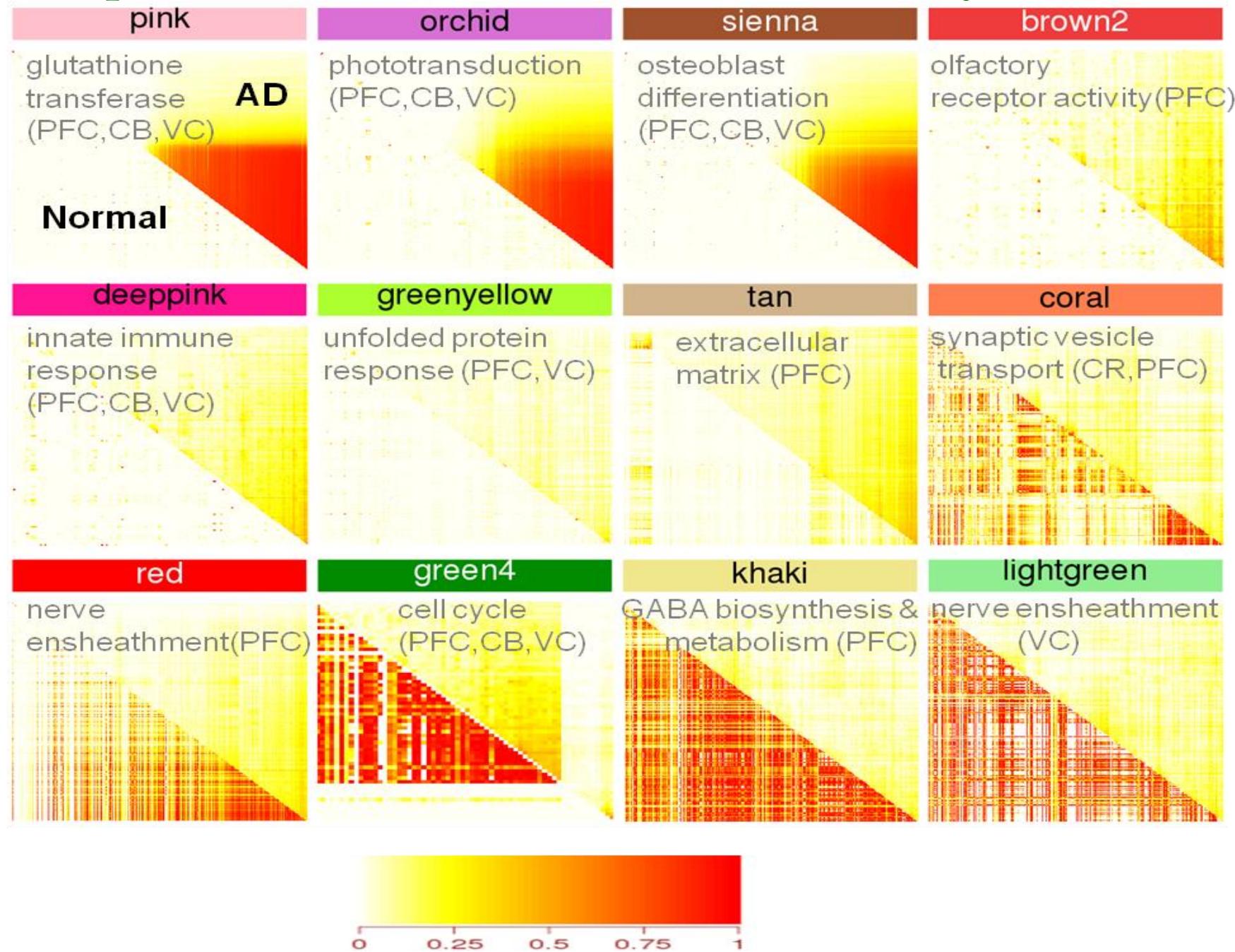
# Multi-Tissue Gene Coexpression Network in AD



# Identification of AD-Specific Gene Networks



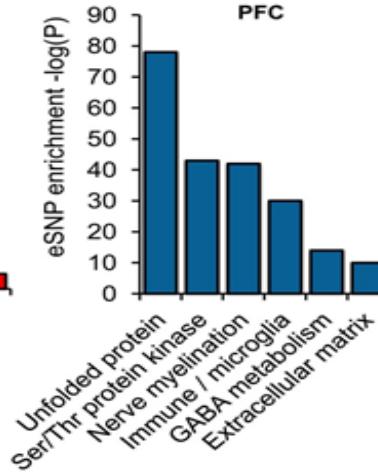
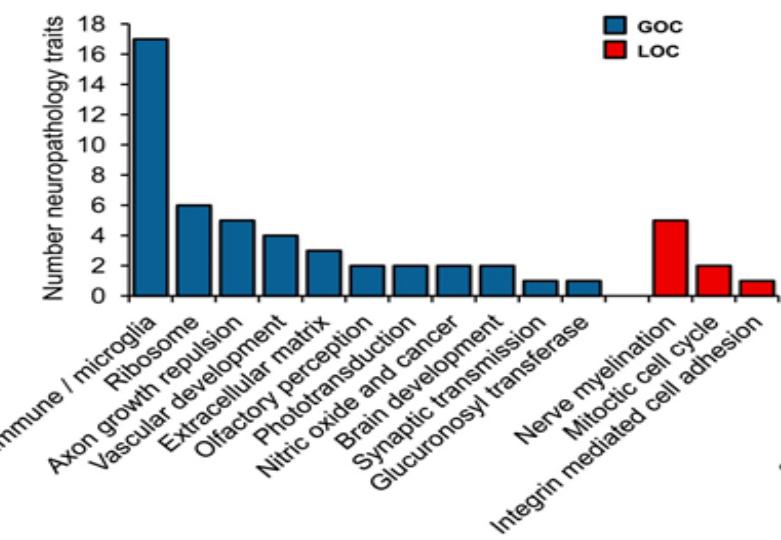
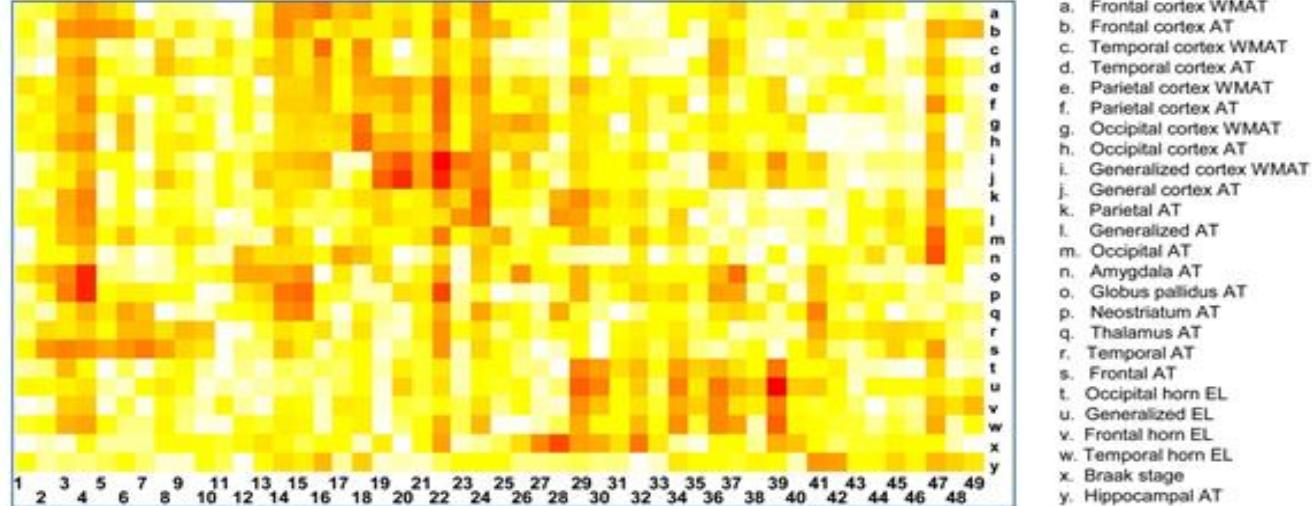
# Comparative/Differential Gene Network Analysis



# Functional Verification of the Modules Associated with AD

- The postsynaptic density proteome in the human neo-cortex of 748 proteins over-represented with risk loci known to underlie cognitive, affective and motor phenotypes are highly enriched in the synaptic transmission AD modules including **the purple (2 fold enrichment, P = 1.4e-16) and salmon (2.5 fold enrichment, P = 5.7e-09)**
- The macrophage-enriched metabolic network or MEMN, is remarkably enriched in all the immune modules of all three tissues, the yellow module in DLPFC (**3.3 fold enrichment, P = 3.3e-98**), **the gold module in CB (7.8 fold enrichment, P = 2.5e-122)** and **the light cyan module in VC (7.3 fold enrichment, P = 3.5e-153)**
- The mouse KO genes from the JAX database showing neurodegenerative related phenotypes, are enriched in two modules with LOC, **khaki (4.1 fold, P = 7.2e-05)** and **blue (1.9 fold, P = 8e-04)**, enriched for the GABA biosynthesis pathway.
- The khaki module is significantly enriched for the 44 most strongly associated genes (**6.6 fold, P=3.5e-3**) listed in the AlzGene database ([www.alzgene.org](http://www.alzgene.org))

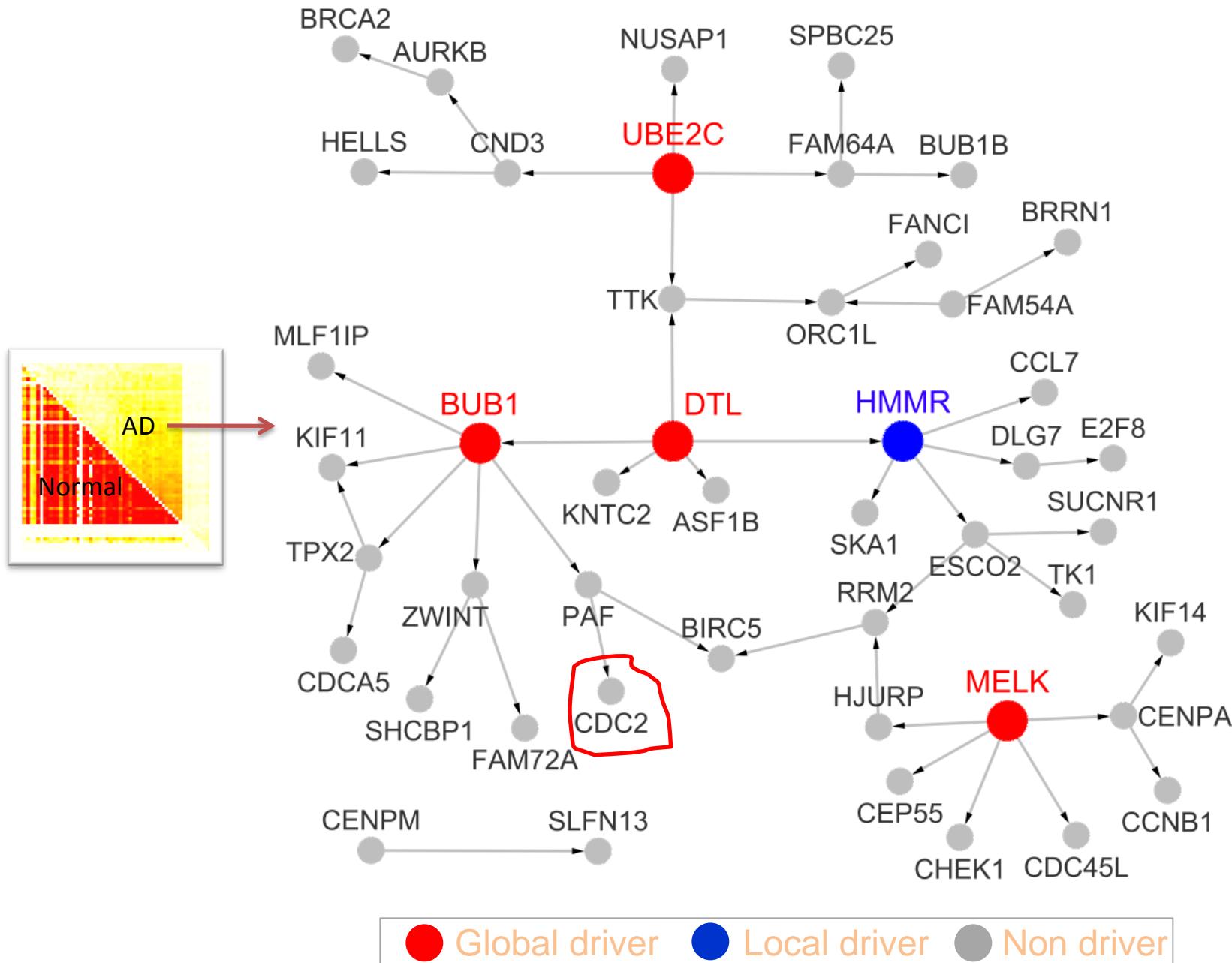
# Module Association with AD Pathology



# PFC Modules most relevant to LOAD Pathology

Module	Rank	Top Functional & Cellular Category	N PFC Genes	MDC	Highlighted Causal Regulators <sup>a</sup>
Yellow	1	Immune & microglia	1102	1,49	TYROBP, DOCK2, FCER1G
Pink	2	Glutathione transferase	113	92,67	GSTA4, ABCC2, TIMELESS
Gray 1	3	Cell junction	51	0,82 <sup>b</sup>	ACBD5, LMAN1, MLL3S
Seashell	4	Coated vesicle	278	1,29 <sup>b</sup>	KIFAP3, PCTK2, SNCA
Red 3	5	Ribosome	50	24,93	RPS27, RPS18, PCBP2
Green yellow	6	Unfolded protein	721	4,50	STIP1, HSPA1A, DOPEY1
Red	7	Nerve myelination & oligodendrocytes	987	0,68	ENPP2, PSEN1, GAB2
Gold 2	8	Axon growth repulsion	80	3,27	TUBB4, ACTL9, ACTG1
Tan	9	Extracellular matrix & choroid plexus cells	700	2,88	SLC22A2, AGTR1, ZIC2
Gold 3	10	Dynein complex	67	12,12	TEKT1, FANK1, HYDIN
Light yellow	11	mRNA cleavage	96	6,01	MED6, STATIP1, SFRS3
Brown 2	12	Olfactory perception	77	25,51	PPP2R5A, C1ORF143, RNASE11
Dark cyan	13	Steroid biosynthesis	110	1,39 <sup>b</sup>	LAMP2, P2RX7, MID1IP1
Khaki	14	GABA biosynthesis & astrocytes	267	0,29	GJA1, STON2, CST3
Grey 60	15	Ser/Thr kinase receptor	495	4,64	CREBBP, ABCC11, MDGA1
Purple	16	Synaptic transmission & neurons	805	1,22	SNAP91, BSN, GLS
Green 4	17	Cell cycle	50	0,33	DTL, UBE2C, BUB1
Honey dew	18	Muscle contraction	128	1,10 <sup>b</sup>	RFX4, DGCR6, AQP4
Red 2	19	Zinc homeostasis	83	1,17 <sup>b</sup>	MT1M, MT1JP, MT1P3
Beige	20	Glucose homeostasis	95	12,64	AMPD1, EGR2, PDGFB

# Dysregulated Cell Cycle Gene Network



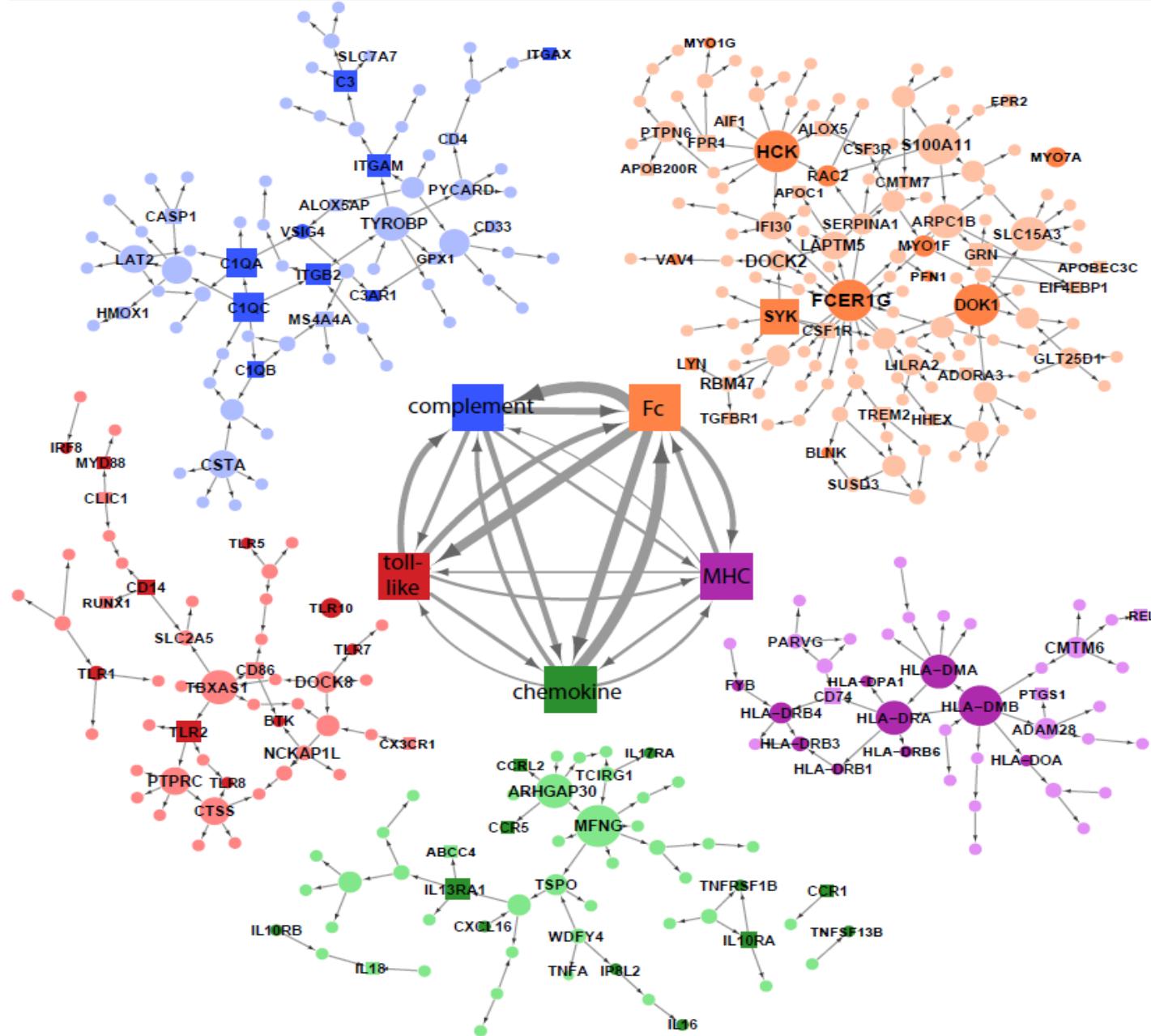
# Relevance of the Predicted Drivers to AD

- The 13 well known AD susceptibility genes (Bertram, McQueen et al. 2007)
- Seven (7) of the 13 known AD susceptibility genes were included in the multi-tissue network
- Three (3) of the 7 genes, CST3,PSEN1 and TF, are the predicted drivers, representing a 5.5-fold enrichment ( $P=1.06e-3$ ) while the rest four are not drivers, i.e., they are underrepresented in the non-driver genes (0.62 fold-enrichment,  $P=0.99$ ).
- The predicted drivers are 9 times more likely to be the known AD susceptibility genes than the non-driver genes.
- The three AD susceptibility driver genes CST3,PSEN1 and TF, are the drivers of the modules with significant loss of connectivity.

# Immune Modules (IMs) as an Effector in AD

- IMs include MS4A4A/MS4A6A, CD33 and TREM2, three genes with risk loci associated with LOAD
- IMs are overrepresented with the disease-associated MEMN and microglia activation pathways
- IMs are most correlated the traits related to LOAD pathology
- The cortex specific IMs show a significant differential connectivity

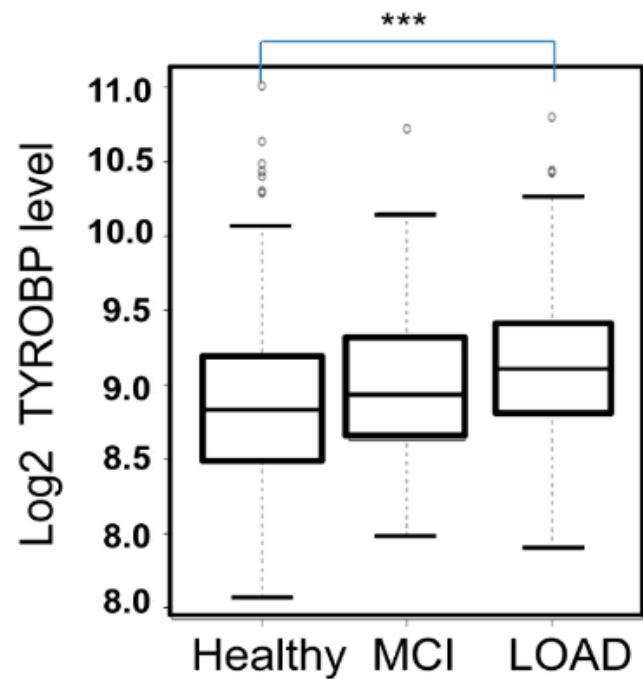
# Immune Response Network in PFC



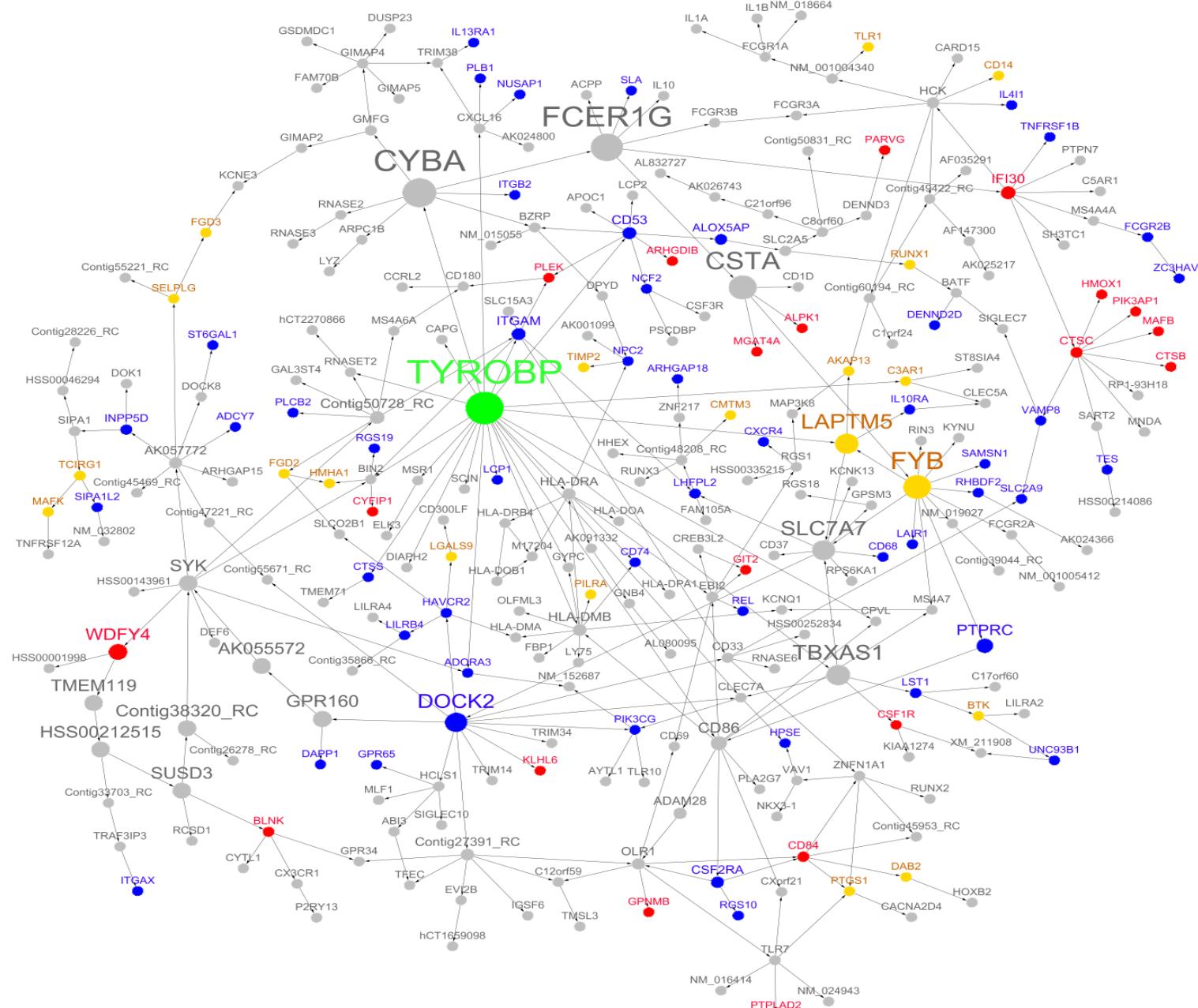
# Causal Regulators of IMs

- CTSC, HCK, TYROBP, SERPINA1, S100A11, LY86, DOCK2 and FCER1G were common to all immune modules, regardless of brain region.
- TYROBP, S100A11 and FCER1G were mapped to the disease associated MEMN in mouse and human populations
- TYROBP is the top driver based on a combined rank order

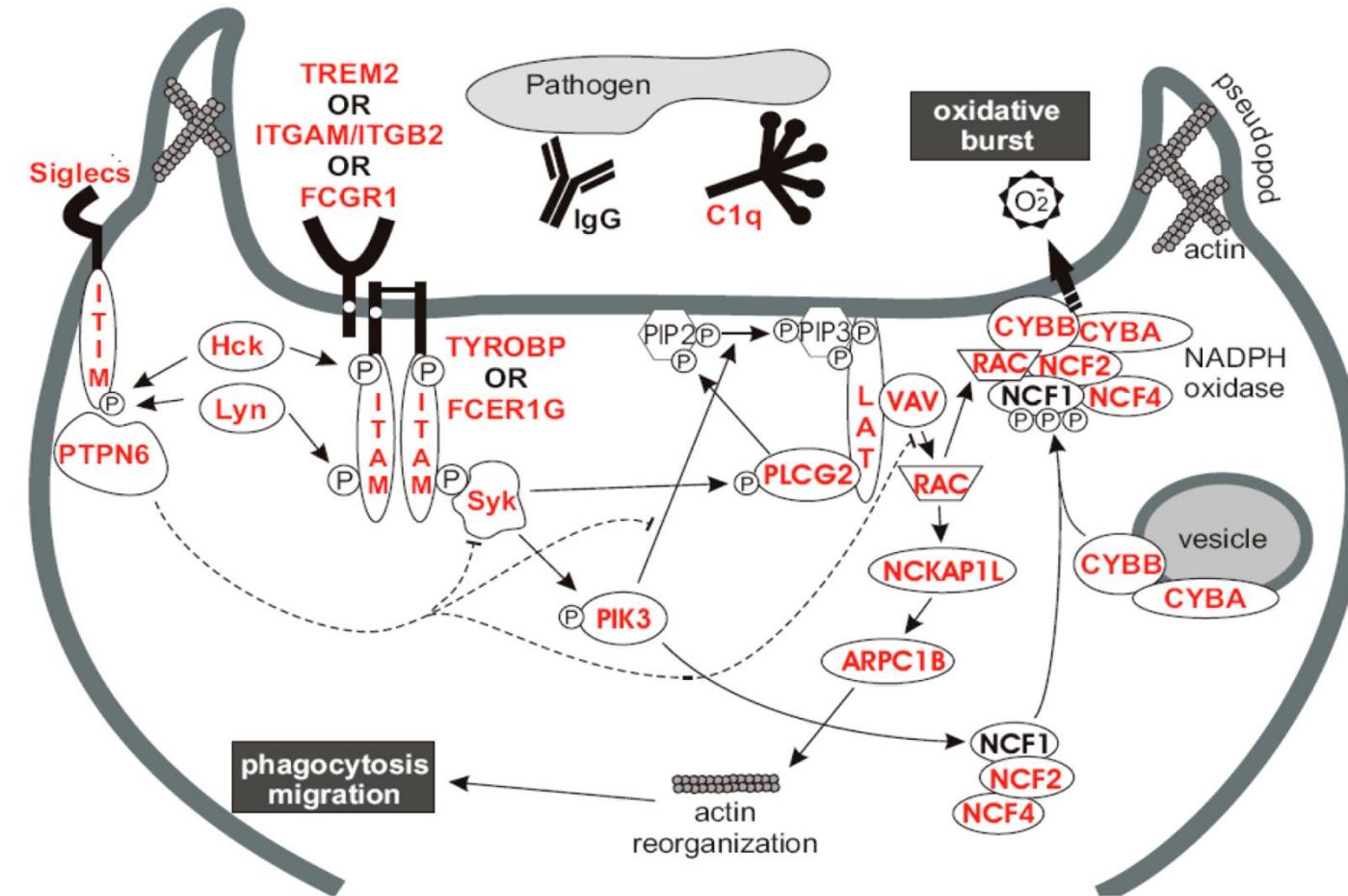
Driver	rank
TYROBP	1
DOCK2	2
HCK	3
FCER1G	4
SERPINA1	5
S100A11	6
CTSC	7
LY86	8



# Validation of TYROBP Networks



# The Microglia Pathogen Phagocytosis Pathway



**ARPC1B** – member of Arp-family  
**CYBA** – p22phox  
**CYBB** – p91phox or NOX2  
**FCER1G** – Fc receptor  $\gamma$   
**FCGR1** – CD64, Fc $\gamma$  receptor I  
**Lyn** – member of Src-family  
**Hck** – member of Src-family  
**ITGAM** – Integrin  $\alpha$ M, Cd11b  
**ITGB2** – Integrin  $\beta$ 2, CD18  
**ITGAM/ITGB2** – complement receptor -3  
  
**NCF4** – p40phox  
**NCF1** – p47phox  
**NCF2** – p67phox  
**NCKAP1L** – member of SCAR/WAVE  
  
**PTPN6** – SHP1  
**PIK3** – PI3K  
**PLCG2** – PLC $\gamma$   
**TYROBP** – DAP12

# Other Important Modules

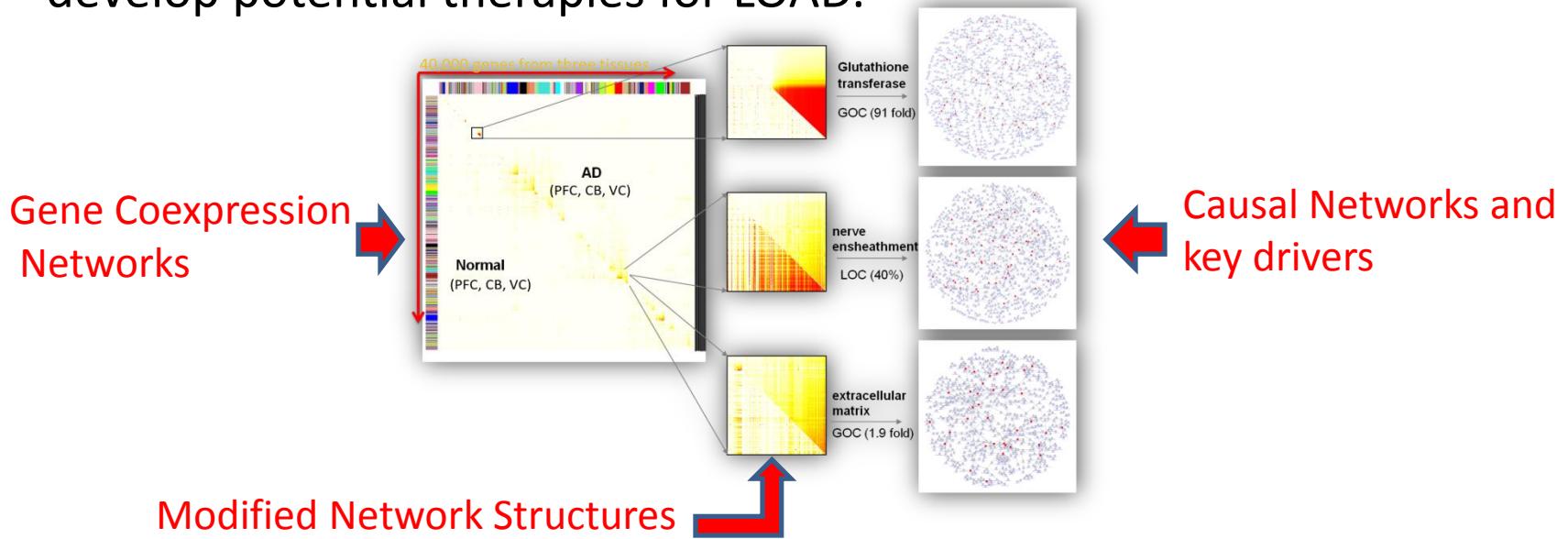
module	module_s	CR_numb	PFC_numb	VC_numb	GO Gene.Category	GO FET_P	GO Fold_E	BACE FET_P	MDC	MDC FDR	Total_Wei	Evidence Nu
yellow		1318	4	1312	2 response to biotic stimulus	1.90E-96	3.25	2.10E-10	1.49	0	21	17
pink		983	90	149	744 glutathione transferase activity	2.10E-03	7.09	8.50E-01	92.67	0	17	15
gray12		52	1	0	51 calcium-dependent cell-cell adhesion	6.80E-03	16.08	6.10E-02	4.26	0.04	14	12
gray1		60	0	60	0 cell junction	2.00E-05	10.42	2.83E-01	0.82	1	11	10
gray17		47	47	0	0 Phagocytosis	2.60E-04	81.57	2.14E-01	1.09	0.34	11	10
seashell		322	0	322	0 cytoskeletal protein binding	4.50E-07	3.2	3.73E-01	1.29	0.16	11	10
cyan		735	5	3	727 response to external biotic stimulus	1.90E-22	2.68	6.90E-04	2.84	0	9	4
cyan4		62	19	24	19 Ribosomal protein	6.80E-05	34.41	1.00E+00	0.85	1	9	8
gray31		36	36	0	0 Exocytosis	1.30E-05	26.57	1.00E+00	0.67	0.88	9	8
gray35		34	5	26	3 fertilization (sensu Metazoa)	9.60E-06	64.87	1.00E+00	4.13	0.62	9	9
green		1217	1211	3	3 nerve ensheathment	6.50E-11	11.56	4.19E-09	0.5	0	9	5
gold2		99	3	96	0 Receptor-mediated axon growth repulsion	4.50E-09	28.34	5.41E-01	3.27	0	8	5
red3		77	3	63	11 Ribosome	6.80E-08	27.56	1.00E+00	24.93	0	8	6
goldenroc		114	39	36	39 Heart development	2.10E-03	29.13	2.34E-01	0.88	1	7	4
gray14		49	20	13	16 mRNA transcription	3.40E-03	293.68	1.00E+00	0.99	1	7	7
gray29		36	1	23	12 B-cell- and antibody-mediated immunity	1.40E-03	34.96	1.40E-01	34.85	0	7	6
gray6		53	0	28	25 Antibacterial response protein	4.40E-04	63.56	1.00E+00	1.16	0.46	7	5
greenyellow		861	0	859	2 response to unfolded protein	8.70E-15	10.43	3.85E-01	4.15	0	7	4
red		1189	1	1188	0 nerve ensheathment	1.50E-08	10.11	7.75E-05	0.68	1	7	4
turquoise		1741	5	32	1704 oxidoreductase activity, acting on the CH-	5.20E-05	8	9.86E-01	2.79	0	7	3
blue		1673	14	20	1639 Cadherin	2.70E-12	4.24	2.09E-07	0.92	1	6	3
gray18		46	46	0	0 Vitamin biosynthesis	1.80E-04	97.89	1.00E+00	3.82	0.02	6	4
gray21		44	44	0	0 odorant binding	9.90E-05	31.24	1.00E+00	1.19	0.32	6	6
gray7		53	0	53	0 protein processing	8.70E-04	15.58	2.41E-01	1.8	0.14	6	5
lightcyan		624	3	9	612 defense response	2.10E-87	4.46	1.32E-14	2.01	0	6	2
lightyellow		506	362	127	17 mRNA cleavage factor complex	3.40E-04	20.74	9.09E-01	6.09	0	6	2
tan		830	0	830	0 extracellular region	3.00E-38	2.89	8.61E-17	2.88	0	6	3

module	modulesiz	signature	signature_overlap	fold_change	pvalue	members
green	1099	Oligodendrocyte	54	38	10.13294915	1.11E-33 AATK,ABCA2,ANLN,APOD,ARHGEF10,CNTN2,C
lightgreen	475	Oligodendrocyte	54	28	17.2748538	2.52E-30 ABCA2,ANLN,CNTN2,DAAM2,EDG8,FA2H,FRM
red	1091	Oligodendrocyte	54	33	8.864191873	1.66E-26 AATK,ABCA2,ANLN,CNTN2,DAAM2,EDG8,FA2H
purple	847	Neuron	43	26	11.2970539	3.67E-24 ADD2,ATP6V1G2,BEX2,CAMK2A,CHGB,CHN1,C
yellow	1175	Microglia	105	43	5.51550152	9.13E-23 ADM,ADORA3,AIF1,AQP9,CCL2,CISH,CXCL1,CX
gold	400	Microglia	105	26	9.796428571	4.52E-20 ADORA3,AIF1,BIRC3,ETS2,FBP1,FCGR1A,FCGR2
lightcyan	559	Microglia	105	28	7.549194991	2.03E-18 A2M,ACP5,ADORA3,AIF1,FBP1,FCGR1A,FCGR2
blue	1508	Astrocyte	31	22	7.447377428	1.05E-17 ALDOC,APOE,AQP4,ATP1A2,BCAN,CLU,CSPG3,CST3,DI
magenta	841	Astrocyte	31	18	10.92593303	3.85E-17 APOE,AQP4,ATP1A2,BCAN,CLU,CSPG3,CST3,DI
khaki	274	Astrocyte	31	12	22.35695785	1.48E-15 ALDOC,APOE,AQP4,ATP1A2,CSPG3,CST3,EDG1
red4	62	ChoroidPlexus	73	10	34.9646487	3.87E-15 ABCA4,CLDN1,FOLR1,KL,MSX1,PRLR,SLC39A12,
salmon	751	Neuron	43	17	8.330752795	2.43E-13 CAMK2A,CHN1,CHST1,CLSTN3,CPLX1,CX3CL1,C
tan	737	ChoroidPlexus	73	21	6.176929797	9.94E-13 ABCA4,CFH,COL8A1,COL8A2,F13A1,KDR,LEPR,I
coral	454	Neuron	43	13	10.53811085	7.68E-12 CPLX1,JAKMIP1,NAPB,NEFL,PACSIN1,PTPRN,R

transmission of nerve impulse

# Summary

- Developed **multiscale network based models** for Late Onset Alzheimer's Disease (LOAD).
- Revealed multiple aspects of **molecular modifications** in LOAD across **multiple brain regions**.
- Identified a **gene network involved in inflammation response** as the top ranked pathway causally linked to LOAD.
- Identified and validated ***TYROBP*** as a key driver of the inflammation response network that includes the recently discovered ***TREM2*** and several other AD susceptibility genes.
- **The multiscale networks and drivers** provided valuable insights to develop potential therapies for LOAD.



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- **Liviu-Gabriel Bodea**
- **Harald Neumann**

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- Radu Dobrin
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- Eugene Fluder
- Tao Xie
- Joshua McElwee
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- Stacey Melquist
- Manikandan Narayanan

University of Miami

- Amanda J. Myers

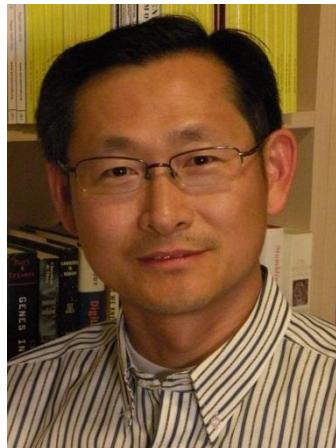
Fred Hutchinson  
Cancer Research  
Center

- Bruce Clurman



# Multiscale Network Modeling Laboratory

<http://research.mssm.edu/multiscalenetwork>



**Dr. Bin Zhang (PI)**  
Assoc. Professor

## Group Members



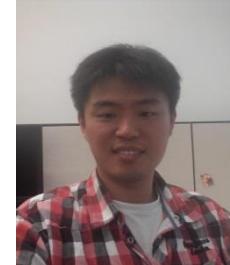
**Dr. Christian Forst**  
Assist. Professor



**Dr. Yongzhong Zhao**  
Senior Scientist



**Dr. Xiandong Lin**  
Scientist



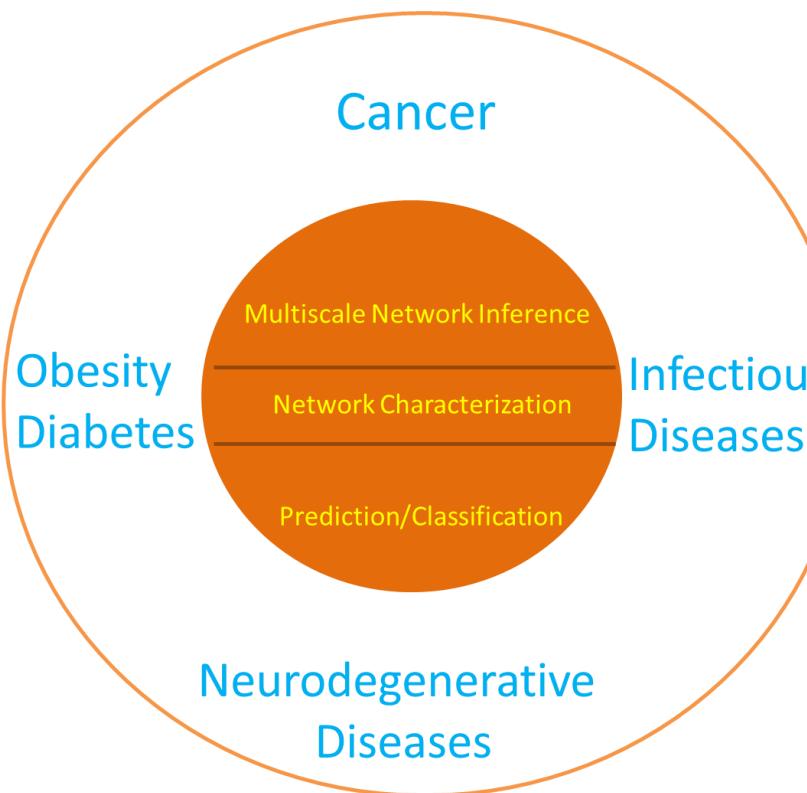
**Dr. Won-min Song**  
Postdoc Fellow



**Igor Katsyv**  
PhD Student



**Andrew McKenzie**  
PhD Student



**Openings for**  
Postdoctoral Fellow &  
Senior Scientist Positions in  
Computational Neuroscience &  
Cancer Biology

<http://research.mssm.edu/multiscalenetwork/Opportunities.html>

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An aerial photograph of a city skyline under a clear blue sky. Overlaid on the image is a white square containing a colorful molecular structure diagram with red, blue, and grey spheres connected by lines. Below this graphic, the text "Icahn Institute" is displayed in a large, bold, white font, followed by the handle "@IcahnInstitute" in a smaller white font. At the bottom of the image, there is descriptive text in white: "The Icahn Institute for Genomics and Multiscale Biology at Mount Sinai integrates the digital universe to better diagnose and treat disease." and the website "icahn.mssm.edu".

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