Syllabus Updates

Principles and Applications of Systems Biology

Vassily Hatzimanikatis

November 2024

EPFL

Syllabus

Date	Lecture	Exercise
14.09	Introduction to Systems Biology	-
20.09	FBA, Objective functions, Growth trade off (FAB1) Phenotypic phase plane, alternative flux distributions (FBA2),	-
27.09	Practical (Software; Simulation exercises)	Q/A MATLAB,Python
04.10	(From 20.09) + Thermodynamics flux balance analysis, and GCM (TFA2)	Q/A
11.10	Thermodynamics flux balance analysis, and GCM (TFA2)	Q/A
18.10	Thermodynamics flux balance analysis, and GCM (TFA2)	
01.11	Data integration of Stoichiometric models	Q/A
08.11	Enzyme kinetics/Large-scale modelling + Kinetic modeling of cancer metabolism	Q/A
15.11	Kinetic modeling of cancer metabolism + Signal transduction systems	Q/A
22.11	ME-models + Communities	Q/A
29.11	(Finish from 22.11) + Work on projects	Q/A
06.12	*Final Presentations*	
13.12	*Final Presentations*	
20.12	-	

Presentation Guide

Presentations should be maximum 20mins.

Your paper presentation should contain:

- Brief introduction to the topic
- Methods used in the paper
- Reproduction and discussion of the results
- Broader impact on the field

From receptors to metabolism: reconstruction, modeling and data integration in signaling networks around metabolism

Principles and Applications of Systems Biology

Vassily Hatzimanikatis

November 2024

EPFL

Introduction to Signaling

Introduction

Proc. Natl. Acad. Sci. USA
Vol. 78, No. 11, pp. 6840–6844, November 1981
Biochemistry

An amplified sensitivity arising from covalent modification in biological systems

(protein modification/metabolic regulation/switch mechanism/enzyme cascades)

ALBERT GOLDBETER† AND DANIEL E. KOSHLAND, JR.

Molecular Cell, Vol. 9, 957–970, May, 2002, Copyright ©2002 by Cell Press

Mathematical Models of Protein Kinase Signal Transduction

Reinhart Heinrich,[1] Benjamin G. Neel,[2]
and Tom A. Rapoport[3,4]

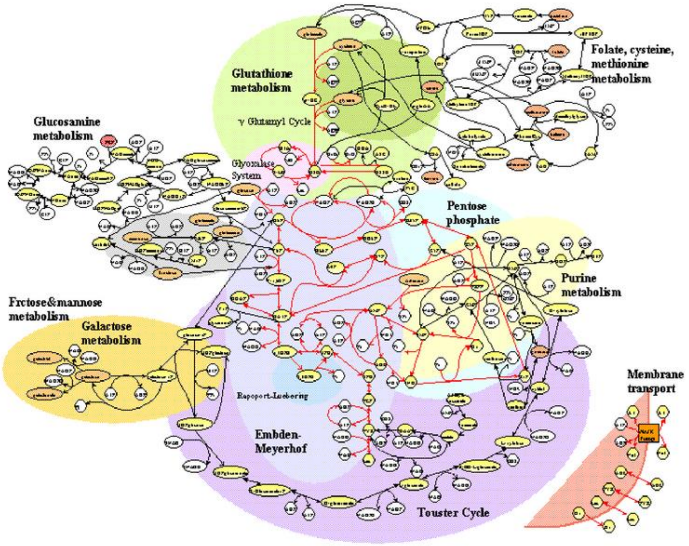
distinct ways to elicit either a
response, which can have dram

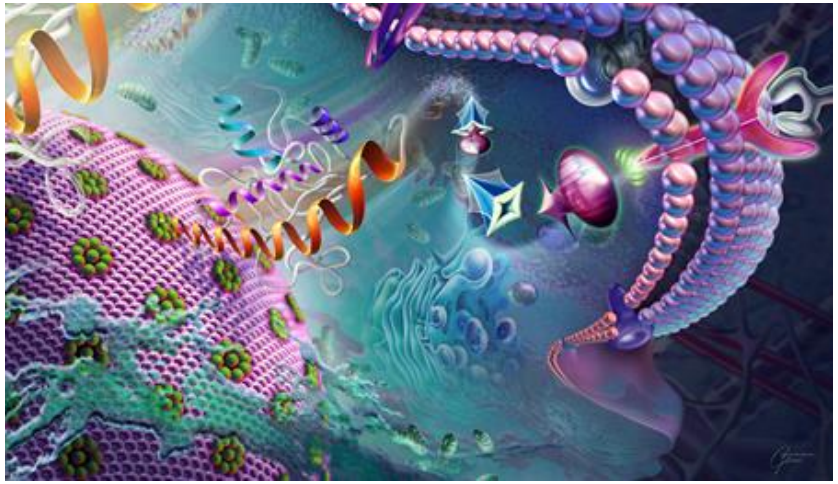
IOP PUBLISHING PHYSICAL BIOLOGY
Phys. Biol. 9 (2012) 045010 (13pp) doi:10.1088/1478-3975/9/4/045010

Exploration of trade-offs between steady-state and dynamic properties in signaling cycles

A Radivojevic[1,2], B Chachuat[3], D Bonvin[2] and V Hatzimanikatis[1]

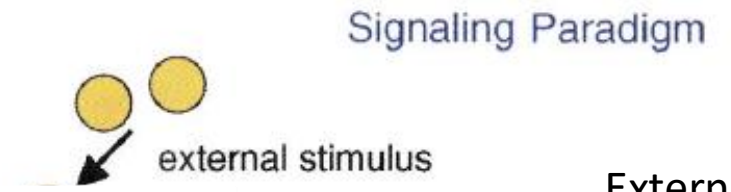
Introduction





Metabolic pathways	Signal transduction pathways
Transfer of mass	Transfer of information
Determined by presence of enzymes catalyzing the reactions	Compounds of different types: highly organized complexes
Metabolites µM - mM	10-10^4 molecules per cell
Enzyme vs. substrate: lower amount of enzyme	Enzyme vs. substrate: same order of magnitude

Introduction

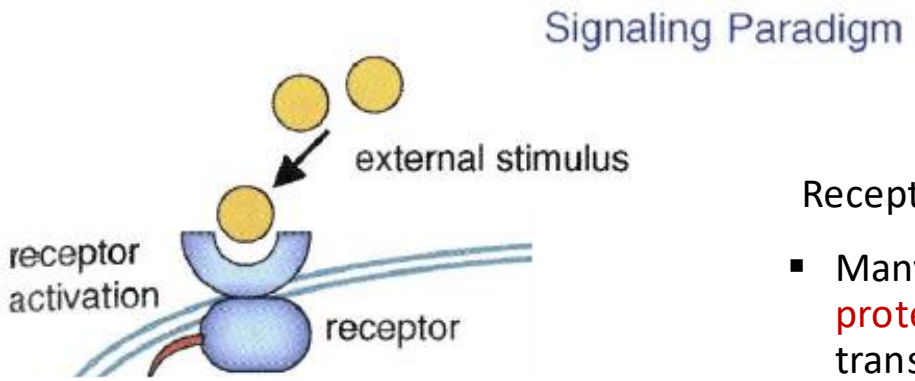


External stimuli:

- hormones
- pheromones
- heat
- cold
- light
- osmotic pressure
- appearance
- Change in concentration of substances

- (glucose, K+, Ca+, cAMP)

Introduction

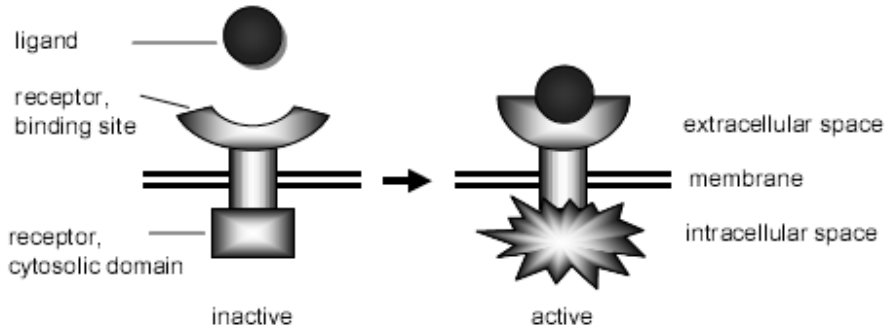


Receptor-ligand interactions:

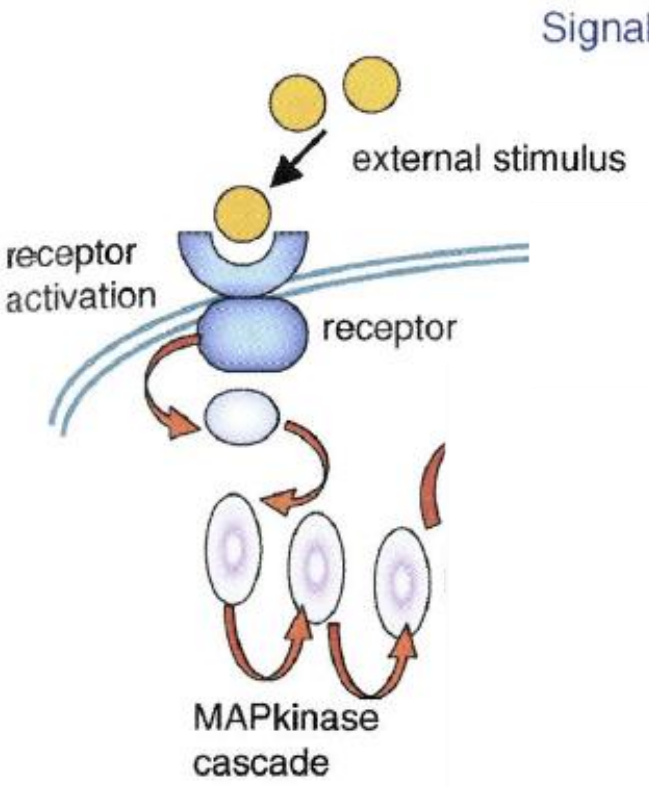
- Many receptors are transmembrane proteins; they receive the signal and transmit it.
- In the active form they are able to initiate a downstream process within the cell

Importing a signal:

- the stimulus may penetrate the cell membrane and bind to a respective receptor in the cell interior.
- Activation of the cytosolic domain

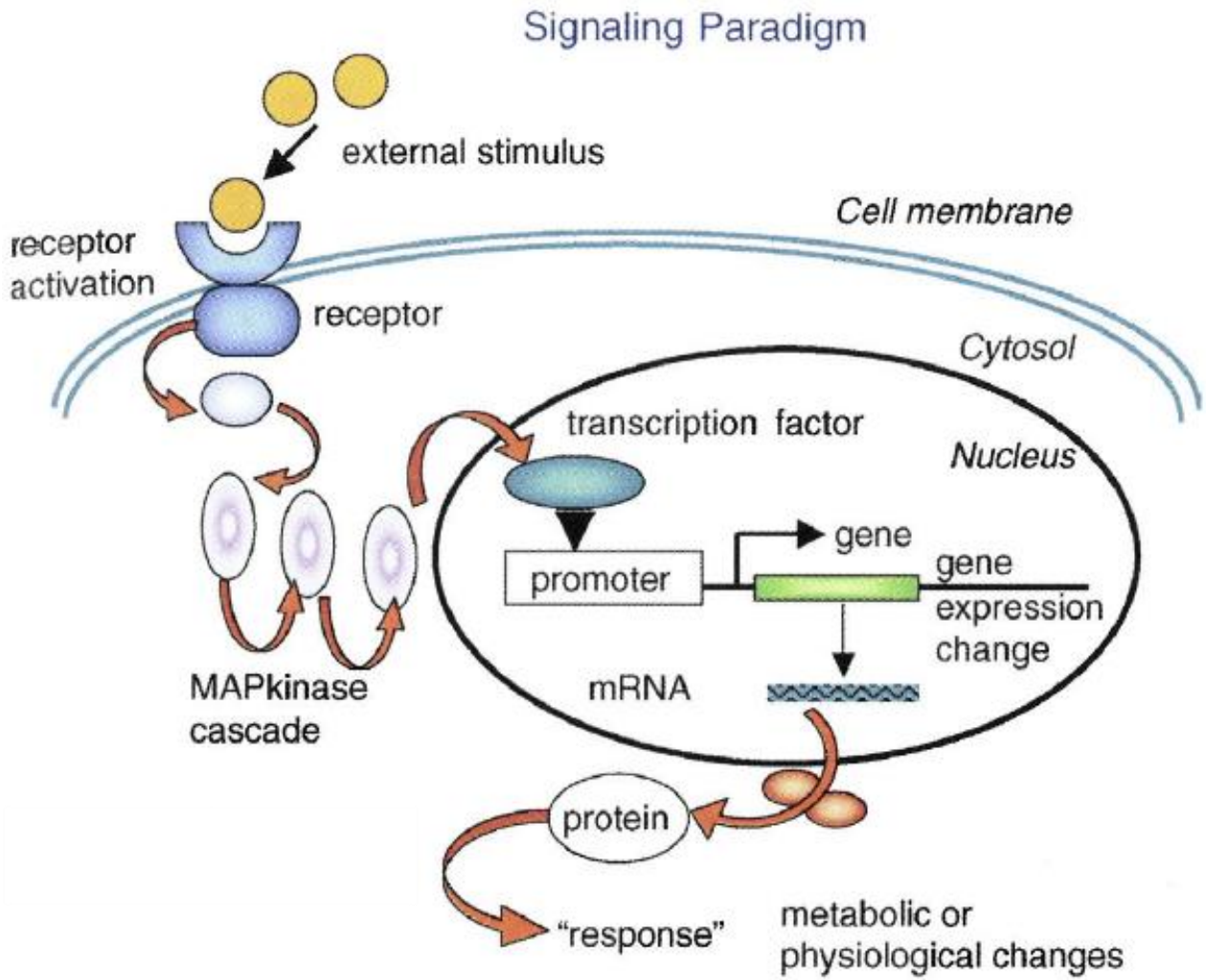


Introduction



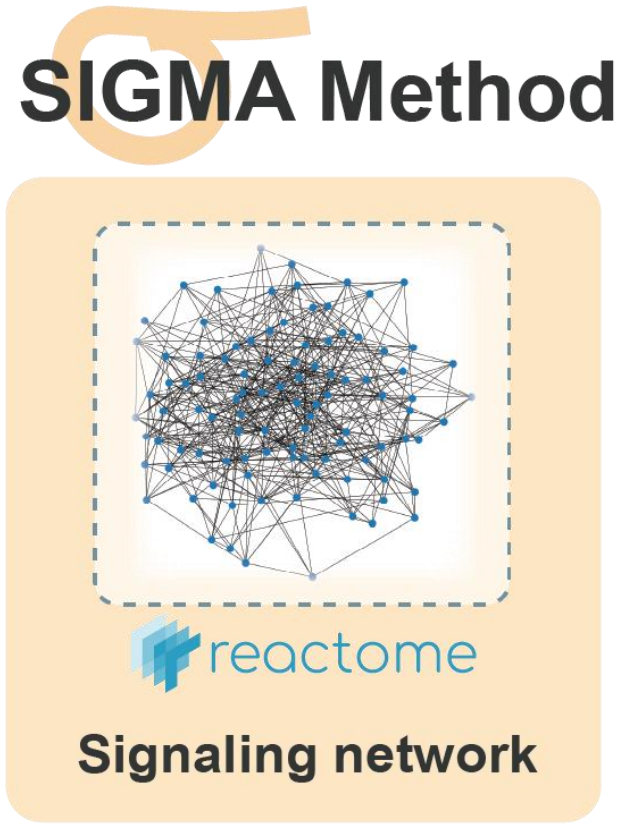
- The active receptor stimulates an internal signaling cascade
- This cascade often includes a series of changes in protein phosphorylation states

Introduction



Introduction to SIGMA method

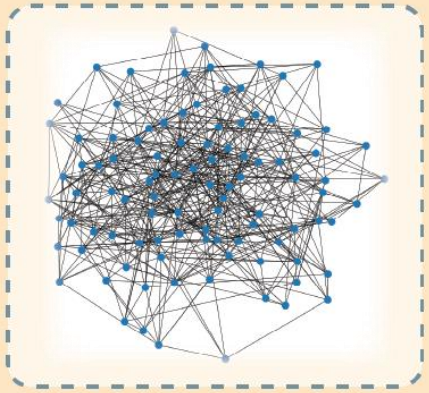
Introduction



- **Reconstruct signaling networks for specific pathways of interest.**

Introduction

SIGMA Method



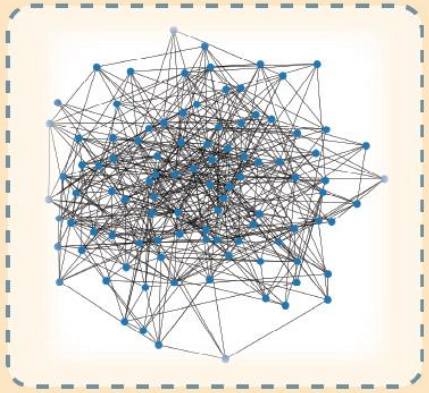
reactome

Signaling network

- **Reconstruct signaling networks for specific pathways of interest.**
- **Navigate the signaling network to study the *information flow*.**

Introduction

SIGMA Method



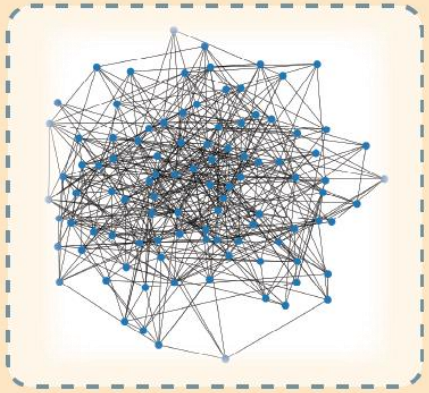
reactome

Signaling network

- **Reconstruct signaling networks for specific pathways of interest.**
- **Navigate the signaling network to study the *information flow*.**
- **Identify the flow of information from receptors to transcription factors or proteins.**

Introduction

SIGMA Method



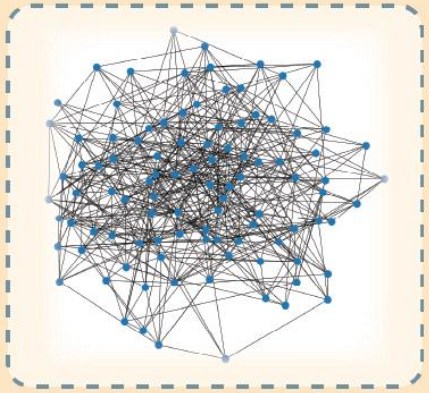
reactome

Signaling network

- **Reconstruct signaling networks for specific pathways of interest.**
- **Navigate the signaling network to study the *information flow*.**
- **Identify the flow of information from receptors to transcription factors or proteins.**
- **Study deregulation in signaling pathways in a consistent manner.**

Reconstruct signaling networks

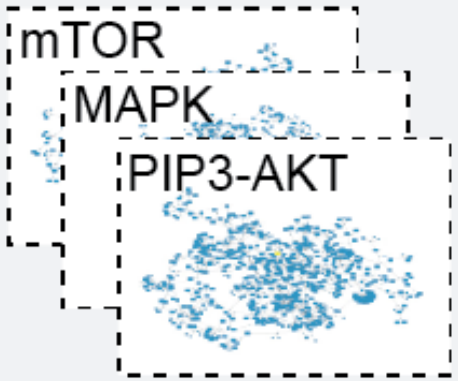
SIGMA Method



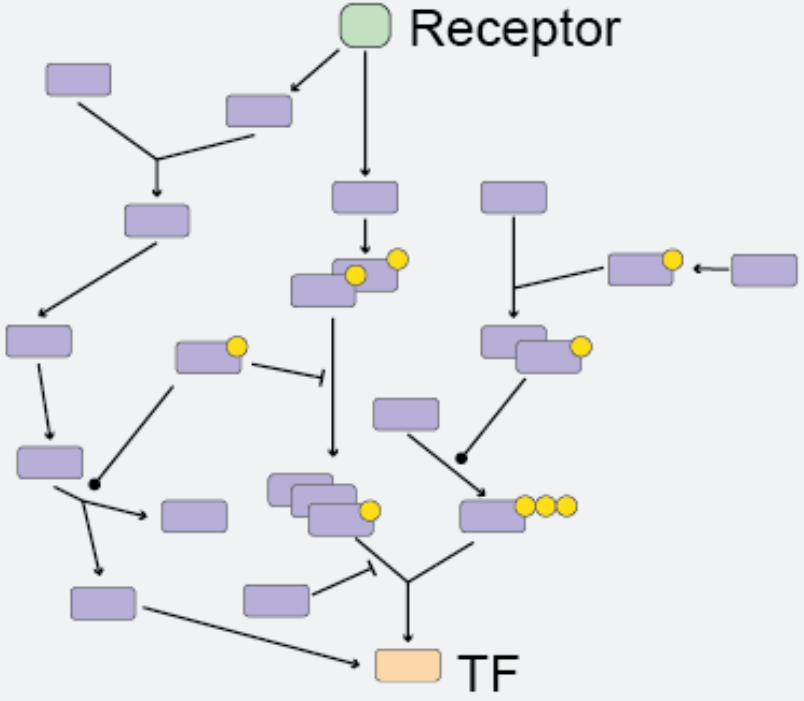
reactome

Signaling network

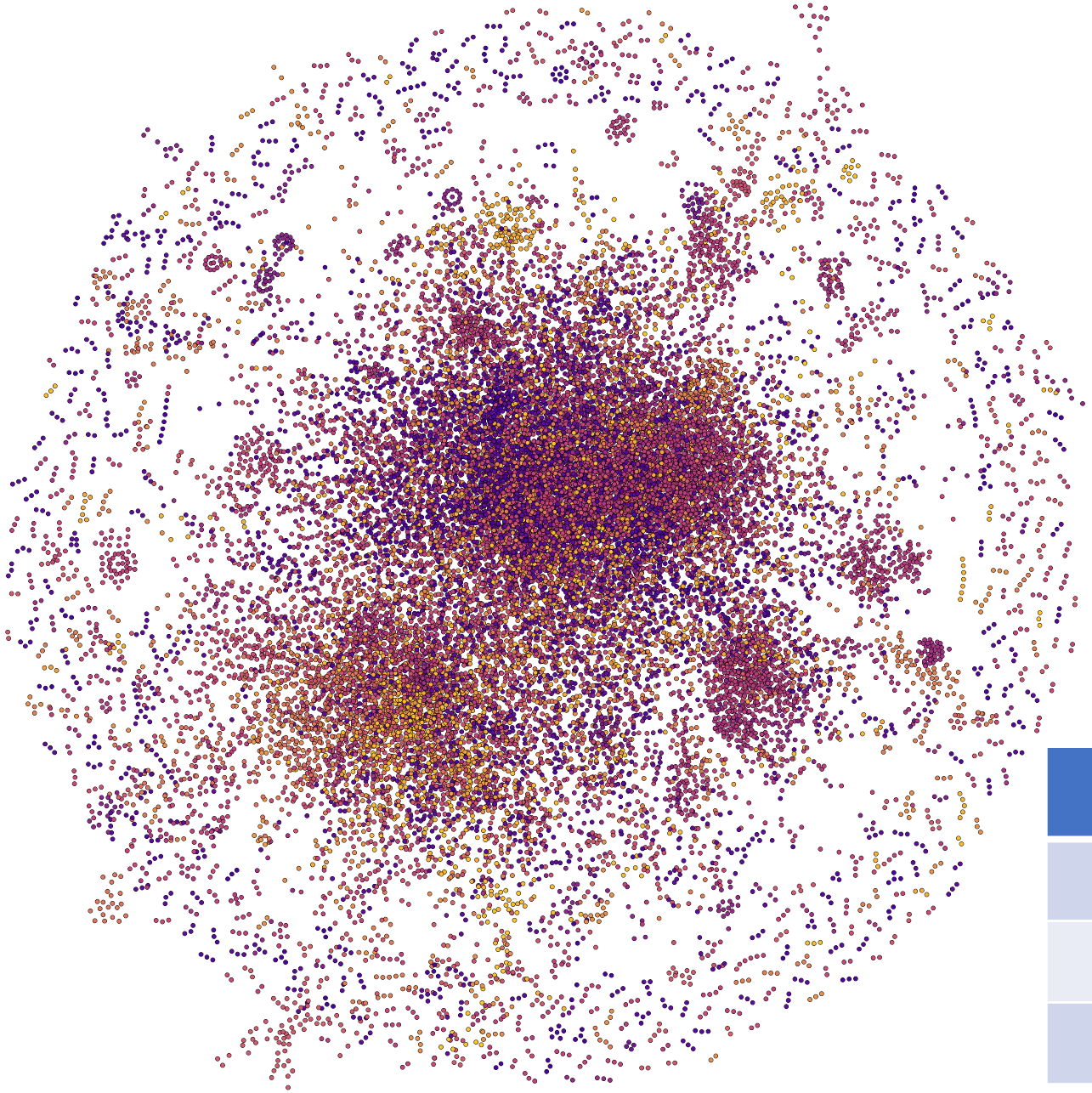
Signaling model



REACTOME signaling pathways



Reactome signaling network



Reactome	
Pathways	2610
Species	23830
Connections	46834

From Reactome to selected pathways network

The need for reconstructing signaling networks around selected pathways.

1) **Allowing manual curation of the selected Reactome pathways.**
2) **Reducing the network size and complexity.**

From Reactome to selected pathways network

The need for reconstructing signaling networks around selected pathways.

1) **Allowing manual curation of the selected Reactome pathways.**
2) **Reducing the network size and complexity.**

Signaling Network Reconstruction Workflow:

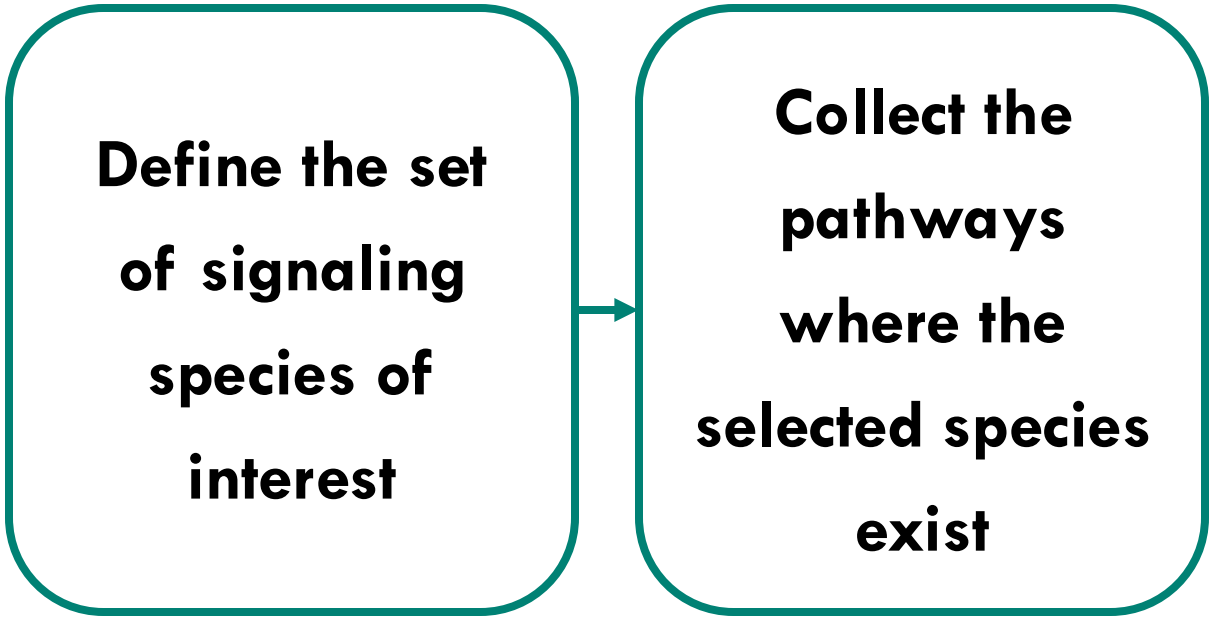
Define the set of signaling species of interest

From Reactome to selected pathways network

The need for reconstructing signaling networks around selected pathways.

1) **Allowing manual curation of the selected Reactome pathways.**
2) **Reducing the network size and complexity.**

Signaling Network Reconstruction Workflow:



From Reactome to selected pathways network

The need for reconstructing signaling networks around selected pathways.

1) **Allowing manual curation of the selected Reactome pathways.**
2) **Reducing the network size and complexity.**

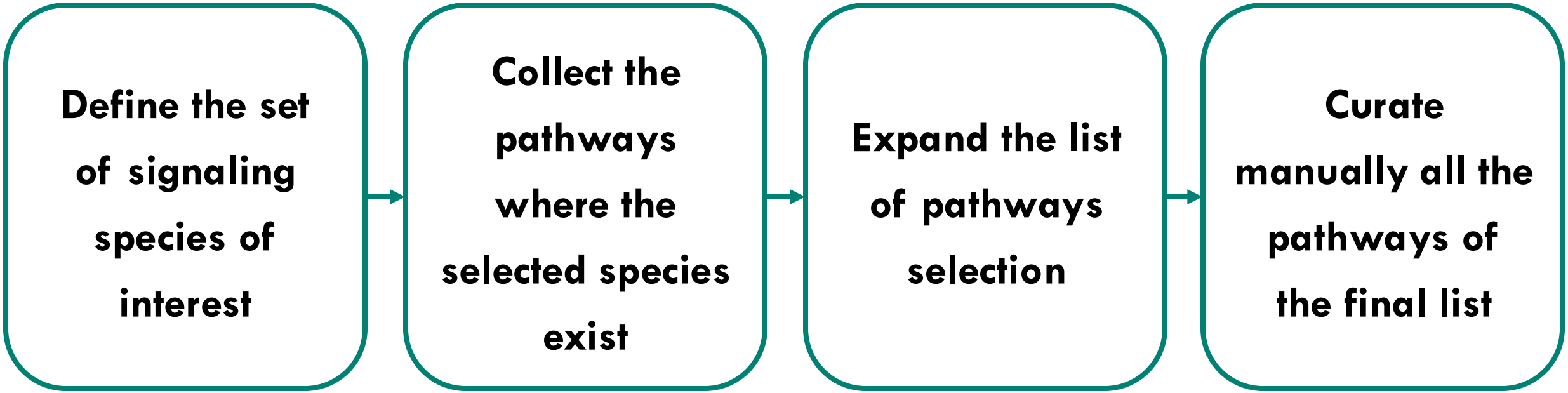
Signaling Network Reconstruction Workflow:

From Reactome to selected pathways network

The need for reconstructing signaling networks around selected pathways.

1) **Allowing manual curation of the selected Reactome pathways.**
2) **Reducing the network size and complexity.**

Signaling Network Reconstruction Workflow:



BDNF signaling in cancer

Received: 18 January 2019 | Revised: 13 April 2019 | Accepted: 18 April 2019
DOI: 10.1002/jcb.29050
RESEARCH ARTICLE
Journal of Cellular Biochemistry WILEY

Brain-derived neurotrophic factor downregulation in gastric cancer

Farbod Esfandi[1] | Hamid Bouraghi[2] | Mark C Glassy[3] | Mohammad Taheri[4] | Mir Salar Kahaei[1] | Vahid Kholghi Oskooei[1] | Soudeh Ghafouri-Fard[1]

ONCOLOGY REPORTS 40: 621-634, 2018

Proliferative role of BDNF/TrkB signaling is associated with anoikis resistance in cervical cancer

YUAN YUAN, HAI-QIONG YE and QIAN-CHUAN REN

Department of Obstetrics and Gynecology, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan 644300, P.R. China

Received October 23, 2017; Accepted May 31, 2018

DOI: 10.3892/or.2018.6515

Received: 10 October 2018 | Revised: 7 April 2020 | Accepted: 20 April 2020
DOI: 10.1096/fj.201802159RRR
RESEARCH ARTICLE
THE FASEB JOURNAL

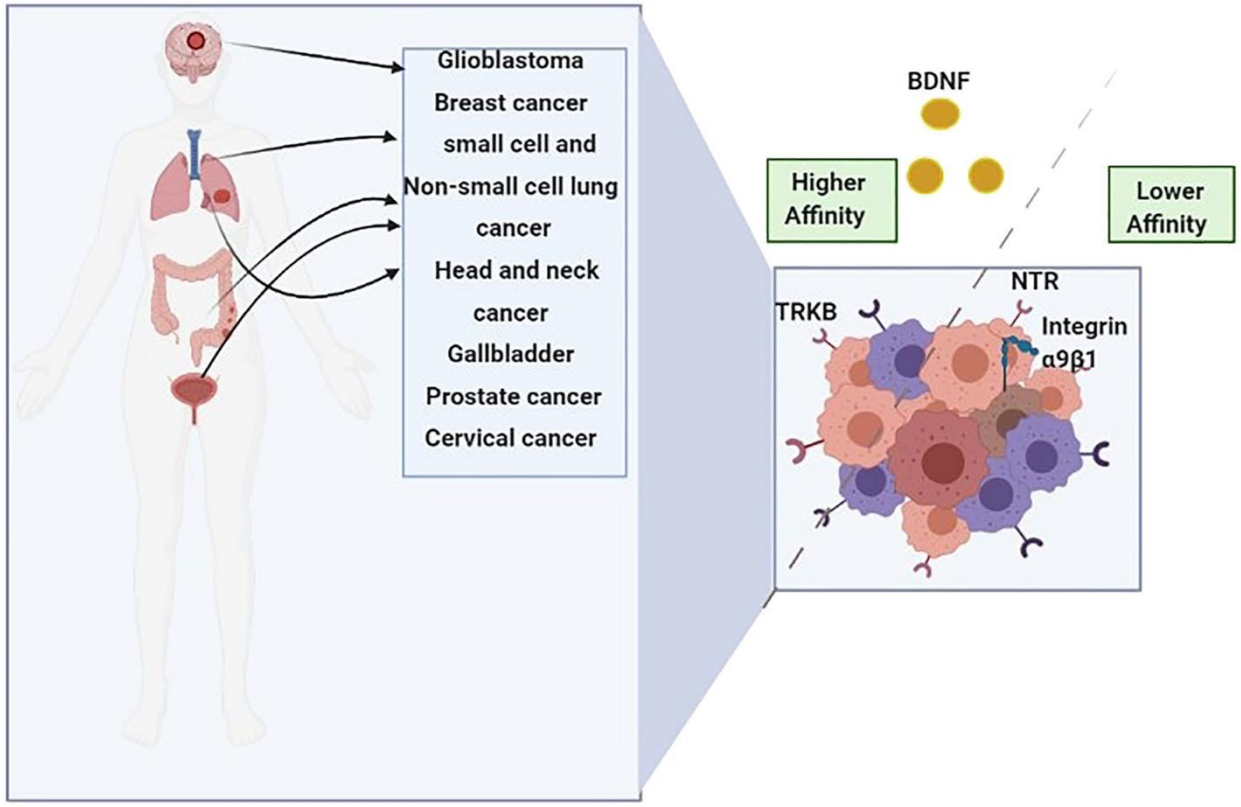
Activation of BDNF/TrkB pathway promotes prostate cancer progression via induction of epithelial-mesenchymal transition and anoikis resistance

Tao Li | Ying Yu | Yarong Song | Xuechao Li | Dongyang Lan | Peng Zhang | Yajun Xiao | Yifei Xing

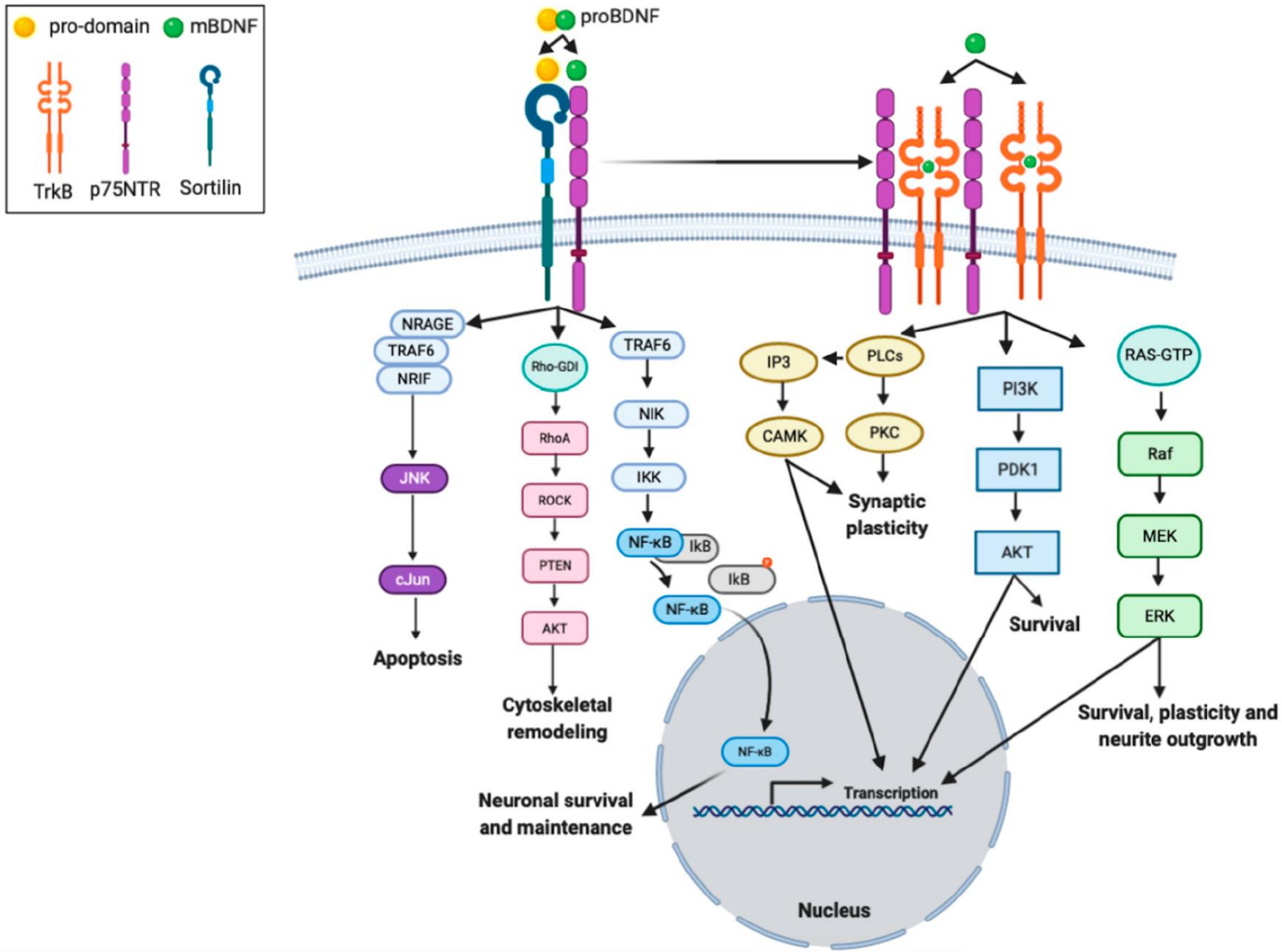
Journal of Cancer Research and Clinical Oncology (2023) 149:2621–2636
https://doi.org/10.1007/s00432-022-04365-8
REVIEW
Check for updates

BDNF and its signaling in cancer

Mohammad Malekan[1,2] · Sasan Salehi Nezamabadi[3,4] · Elham Samami[3,5] · Mehdi Mohebalizadeh[6,7] · Amene Saghazadeh[3,8] · Nima Rezaei[8,9,10]



Brain-derived neurotrophic factor (BDNF)



Colucci-D'Amato, Luca, et. al., *International Journal of Molecular Sciences*, 2020

mTOR signaling in cancer

Review Article | Published: 13 November 2018

mTOR signalling and cellular metabolism are mutual determinants in cancer

Dirk Mossmann, Sujin Park & Michael N. Hall

Nature Reviews Cancer **18**, 744–757 (2018) | Cite this article

Hua *et al. Journal of Hematology & Oncology* (2019) 12:71
https://doi.org/10.1186/s13045-019-0754-1

Journal of Hematology & Oncology

REVIEW Open Access

Targeting mTOR for cancer therapy

Hui Hua[1], Qingbin Kong[2], Hongying Zhang[2], Jiao Wang[3], Ting Luo[4] and Yangfu Jiang[2*]

Zou *et al. Cell Biosci* (2020) 10:31
https://doi.org/10.1186/s13578-020-00396-1

Cell & Bioscience

REVIEW Open Access

mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges

Zhilin Zou[1,2,3†], Tao Tao[4†], Hongmei Li[3*] and Xiao Zhu[1,2*]

International Journal of *Molecular Sciences*

MDPI

Review

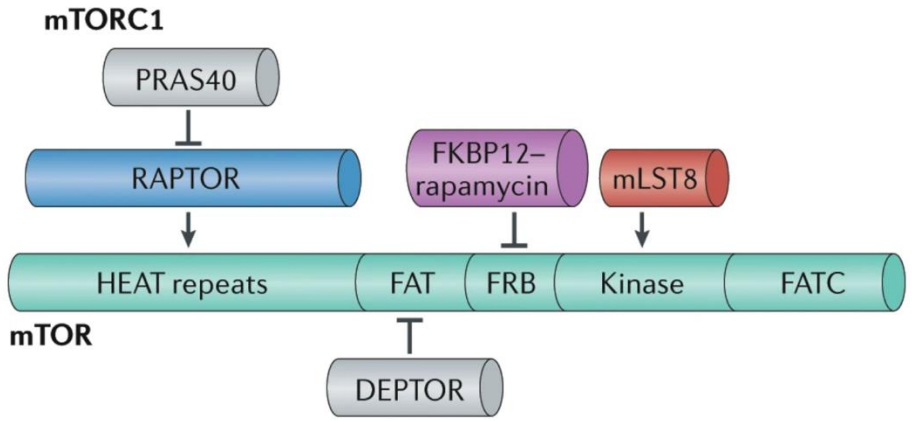
mTOR Signaling in Cancer and mTOR Inhibitors in Solid Tumor Targeting Therapy

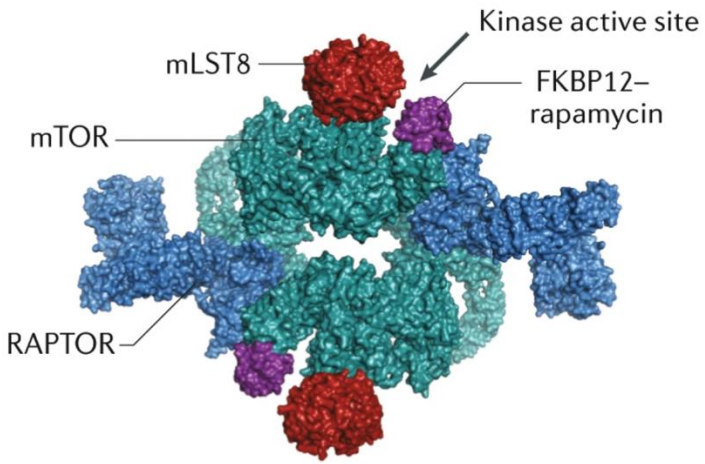
Tian Tian, Xiaoyi Li and Jinhua Zhang *

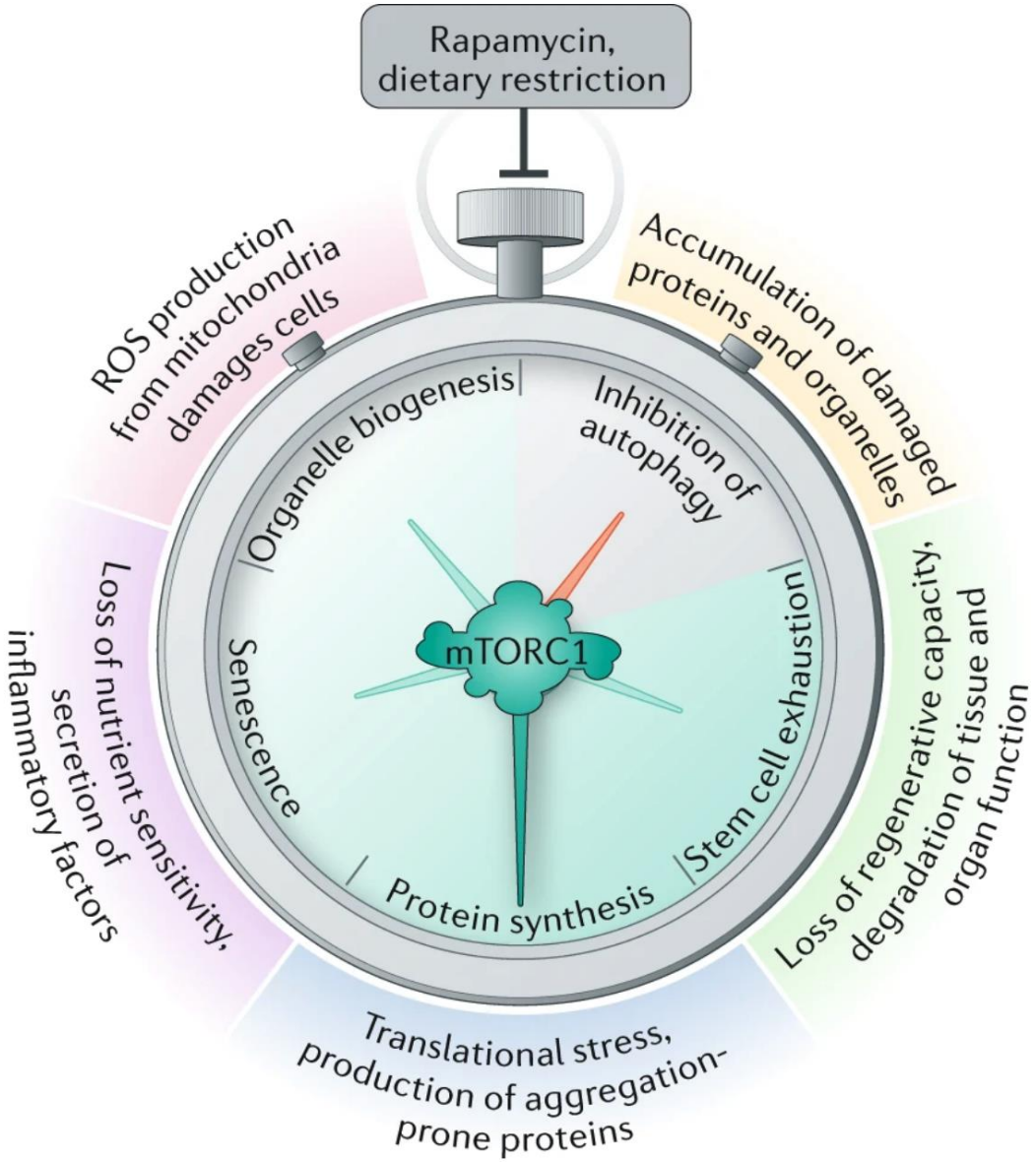
College of Life Science and Bioengineering, Beijing Jiaotong University, Beijing 100044, China; ttian@bjtu.edu.cn (T.T.); 15271074@bjtu.edu.cn (X.L.)
* Correspondence: zhangjh@bjtu.edu.cn; Tel./Fax: +86-10-51684351

Received: 10 January 2019; Accepted: 1 February 2019; Published: 11 February 2019

Mammalian target of rapamycin (mTOR)

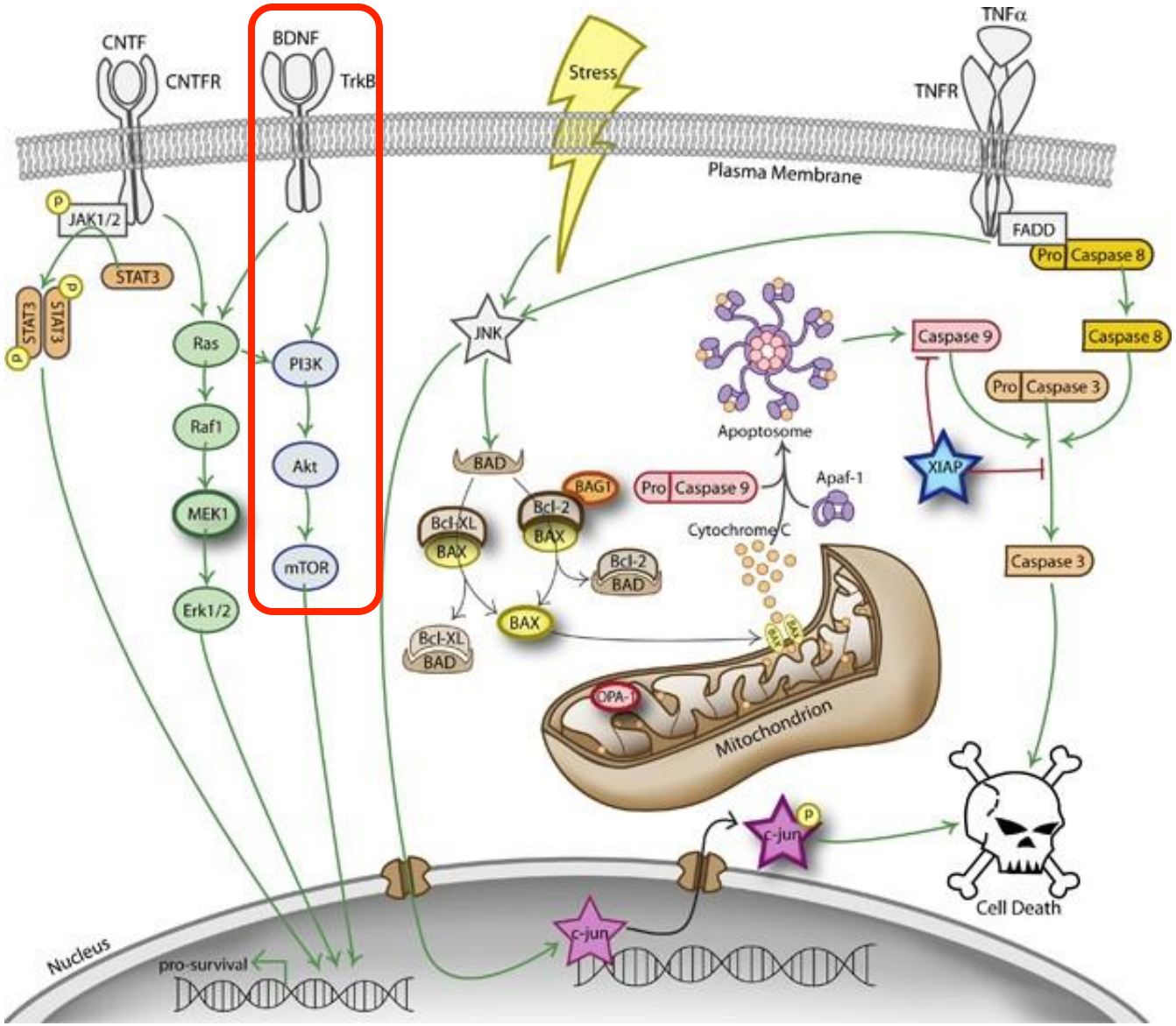






Liu, Grace Y., and David M. Sabatini. "MTOR at the Nexus of Nutrition, Growth, Ageing and Disease." *Nature Reviews Molecular Cell Biology*, 2020

mTOR regulation through BDNF



Wilson, A. M., and A Di Polo, *Gene Therapy*, 2012

AMPK in Cancer

Review Article | Published: 13 March 2019

AMP-activated protein kinase: the current landscape for drug development

Gregory R. Steinberg & David Carling

Nature Reviews Drug Discovery **18**, 527–551 (2019) | Cite this article

OPEN BIOLOGY

royalsocietypublishing.org/journal/rsob

The strange case of AMPK and cancer: Dr Jekyll or Mr Hyde?†

Diana Vara-Ciruelos, Fiona M. Russell and D. Grahame Hardie

Division of Cell Signalling and Immunology, School of Life Sciences, University of Dundee, Dow Street, Dundee DD1 5EH, UK

Yuan *et al. Journal of Hematology & Oncology* (2020) 13:113
https://doi.org/10.1186/s13045-020-00949-4

Journal of Hematology & Oncology

REVIEW Open Access

The MAPK and AMPK signalings: interplay and implication in targeted cancer therapy

Jimin Yuan[1,2*], Xiaoduo Dong[3], Jiajun Yap[4] and Jiancheng Hu[4,5*]

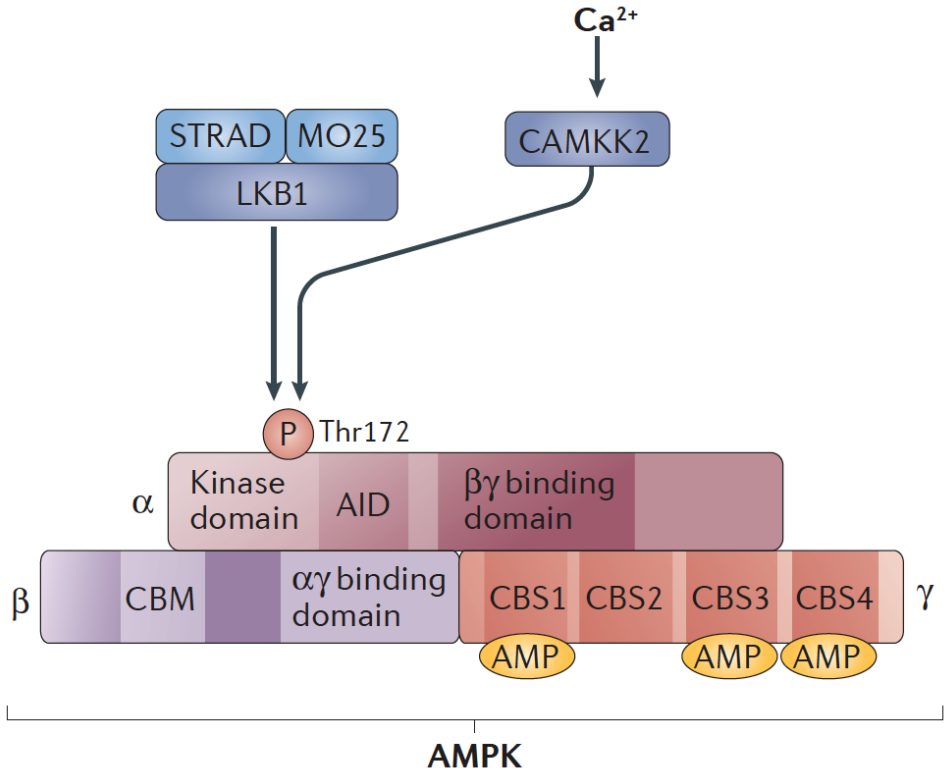
Hindawi
Oxidative Medicine and Cellular Longevity
Volume 2019, Article ID 8730816, 16 pages
https://doi.org/10.1155/2019/8730816

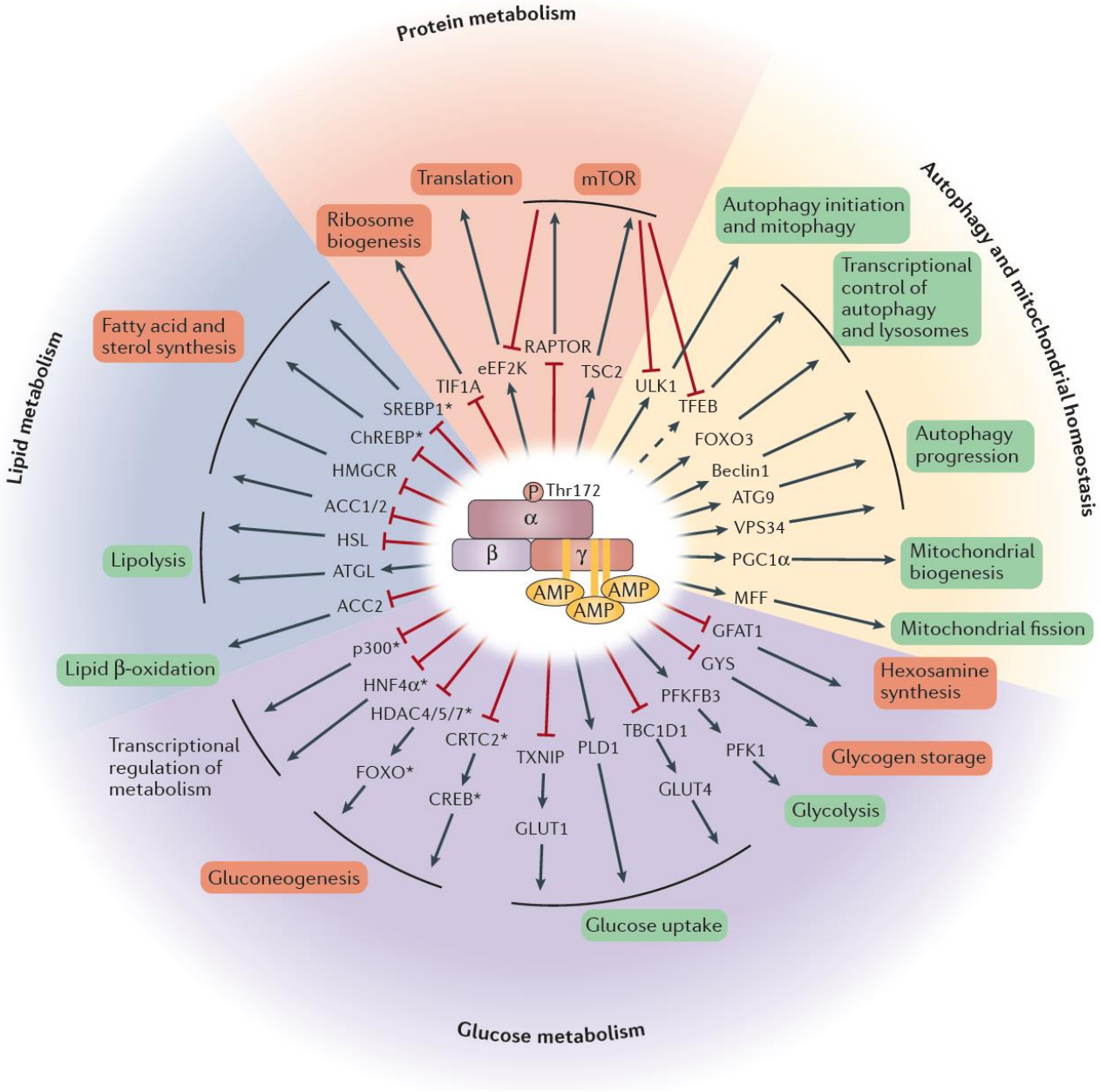
Review Article

LKB1/AMPK Pathway and Drug Response in Cancer: A Therapeutic Perspective

Francesco Ciccarese, Elisabetta Zulato, and Stefano Indraccolo

AMP-activated protein kinase (AMPK)





Herzig, Sébastien, and Reuben J. Shaw. "AMPK: Guardian of Metabolism and Mitochondrial Homeostasis." *Nature Reviews Molecular Cell Biology*, 2018

Signaling network reconstruction

1. Define the set of signaling species of interest

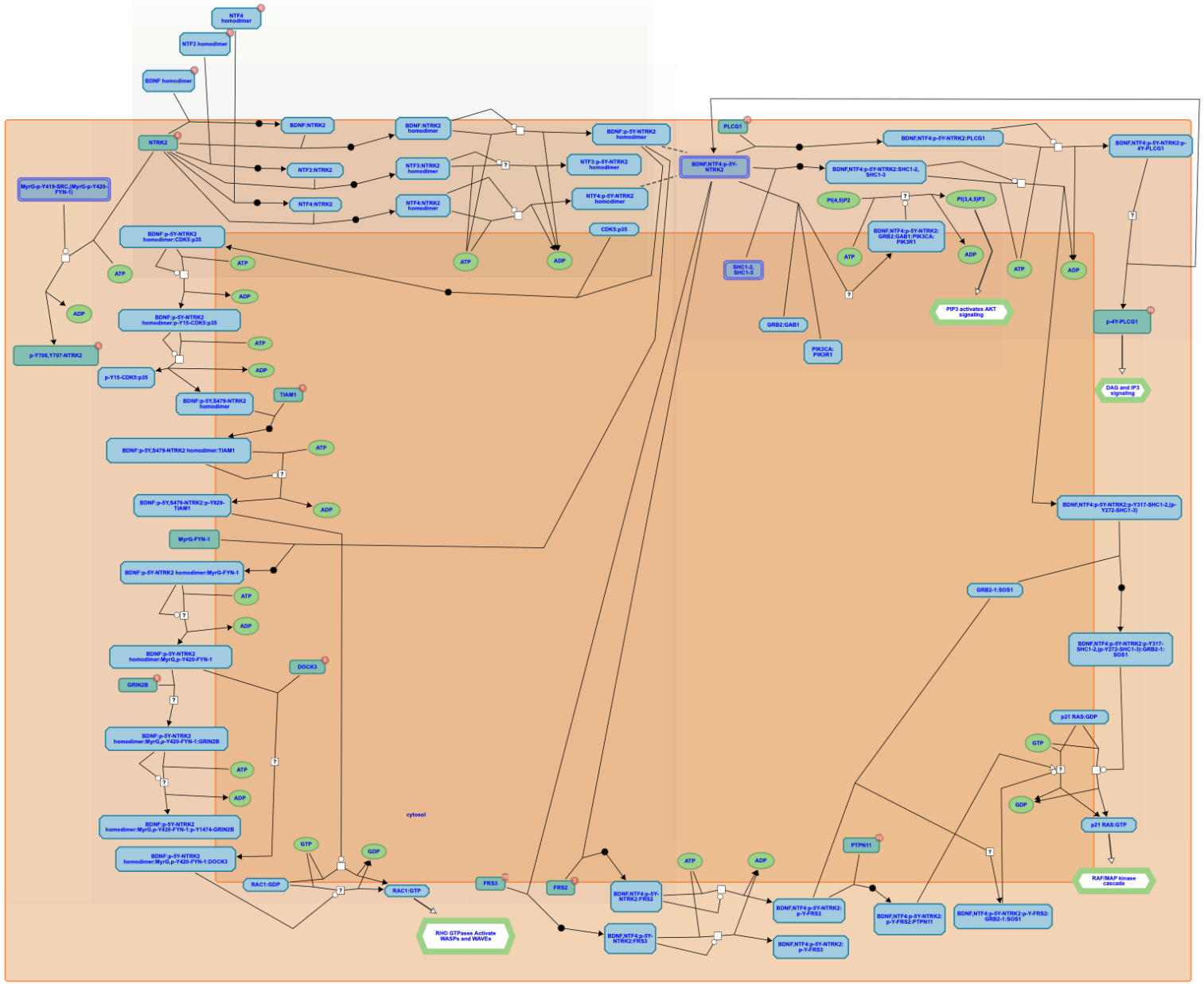
Signaling network reconstruction

1. Define the set of signaling species of interest

- **Brain-derived neurotrophic factor (BDNF)**

BDNF signaling in Reactome

Signaling by Neurotrophic Receptor Tyrosine Kinase 2 (NTRK2)



Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

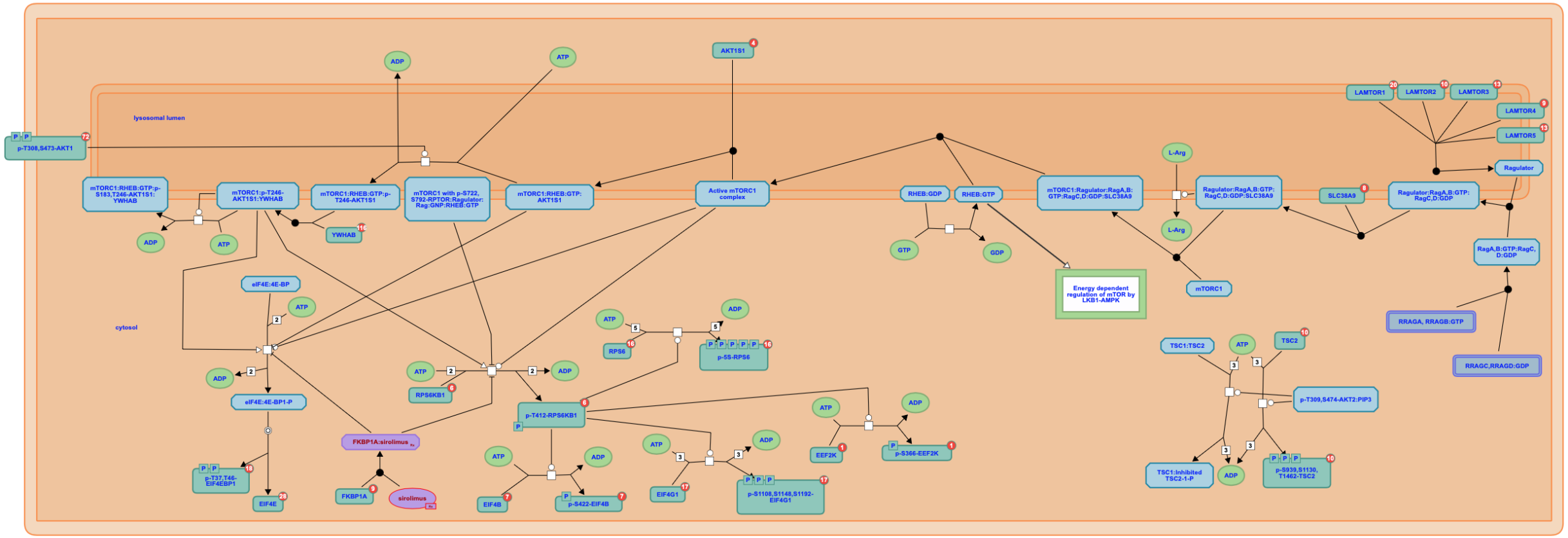
Signaling network reconstruction

1. Define the set of signaling species of interest

- **Brain-derived neurotrophic factor (BDNF)**
- **Mammalian target of rapamycin (mTOR)**

mTOR signaling in Reactome

mTOR signaling



Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

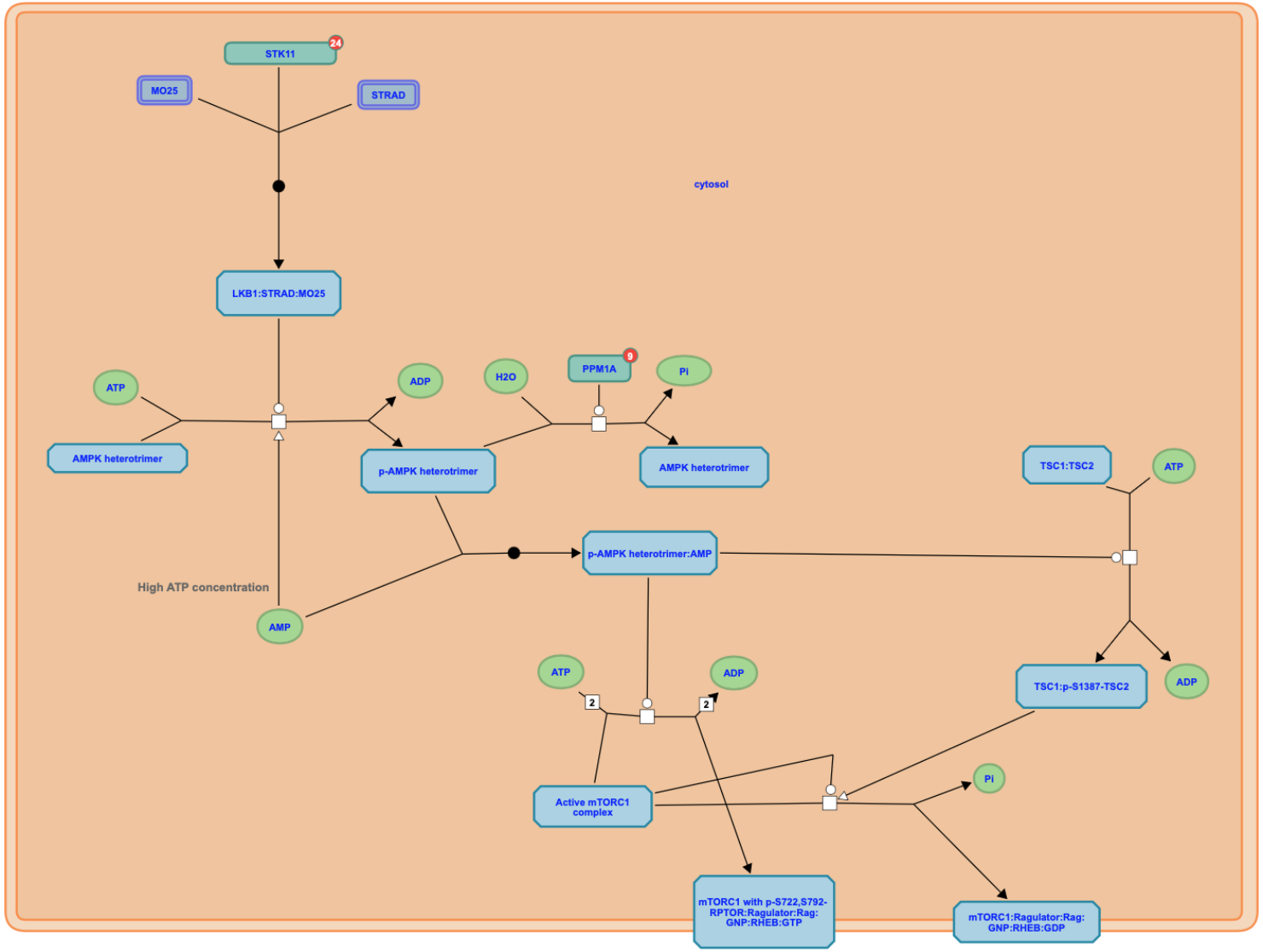
Signaling network reconstruction

1. Define the set of signaling species of interest

- **Brain-derived neurotrophic factor (BDNF)**
- **Mammalian target of rapamycin (mTOR)**
- **AMP-activated protein kinase (AMPK)**

AMPK signaling in Reactome

Energy dependent regulation of mTOR by LKB1-AMPK



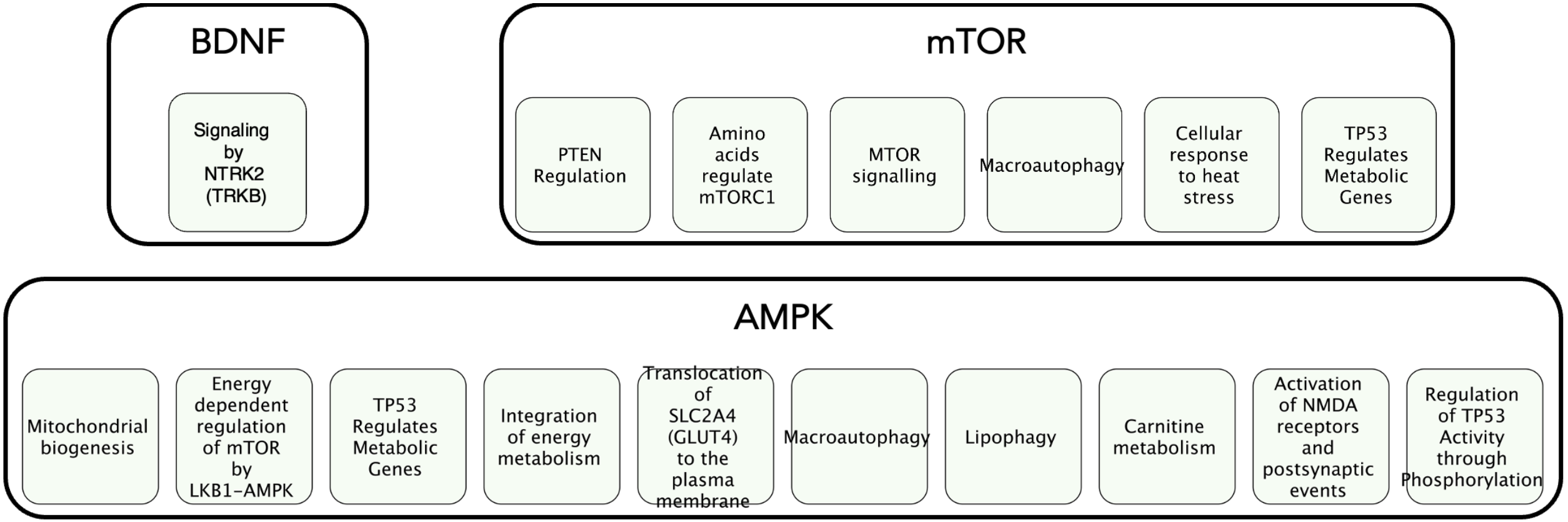
Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

Signaling network reconstruction

2. Collect the pathways where the selected species exist

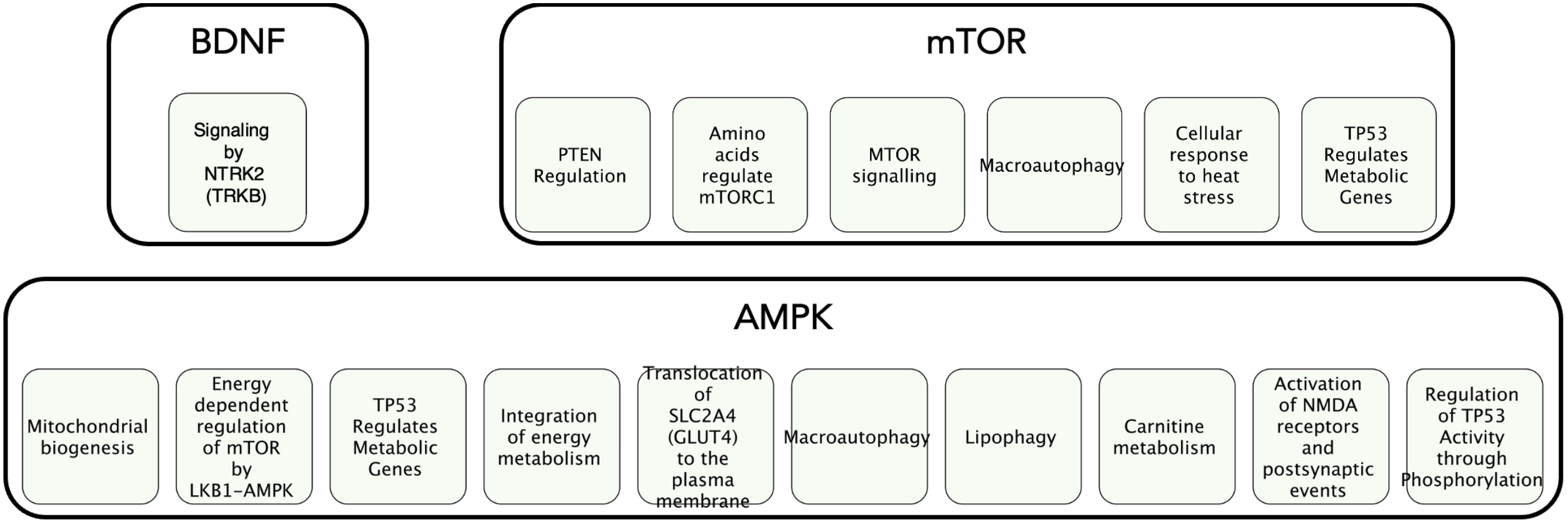
Signaling network reconstruction

2. Collect the pathways where the selected species exist



Signaling network reconstruction

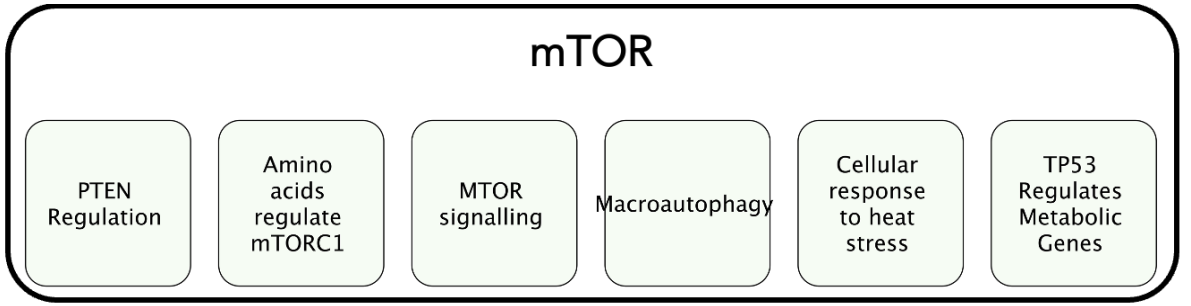
2. Collect the pathways where the selected species exist



The pathway collection is not only based in the original state of the species but also in modified states of the species
(e.g. phosphorylated state, ubiquitinated state, complex component)

Signaling network reconstruction

2. Collect the pathways where the selected species exist



Active mTORC1 complex [l]	mTORC1:Ragulator:RagA,B:GTP:RagC,D:GDP:SLC38A9 [l]
mTORC1 [c]	mTORC1:RHEB:GTP:AKT1S1 [l]
mTORC1 dimer [n]	mTORC1:RHEB:GTP:p-S183,T246-AKT1S1:YWHAB [l]
mTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:GNP:RHEB:GTP [l]	MTORC1:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]
MTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:RHEB:GTP [l]	mTORC1:RHEB:GTP:p-T246-AKT1S1 [l]
MTORC1 with p-S722,S792-RPTOR:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]	MTORC1:RHEB:GTP:ULK1:ATG13:RB1CC1:ATG101 [l]
mTORC1:p-T246-AKT1S1:YWHAB [l]	v-ATPase:Ragulator:RRAGA,B:GDP:RRAGC,D:GDP:mTORC1:RHEB:GTP [l]
mTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]	v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:mTORC1 [l]
MTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]	v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:mTORC1:RHEB:GTP [l]
MTORC1:Ragulator:Rag:GNP:RHEB:GTP [l]	

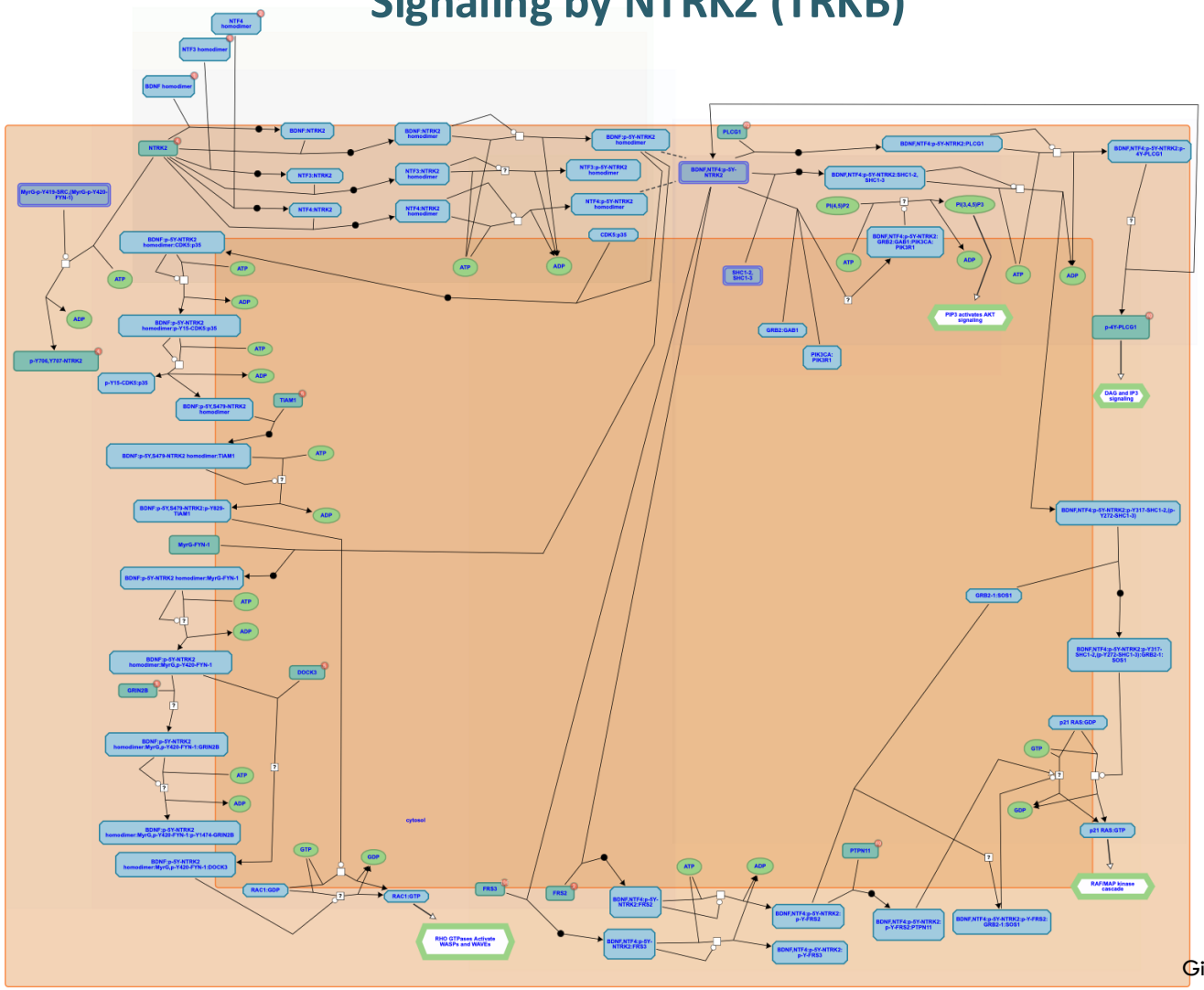
The pathway collection is not only based in the original state of the species but also in modified states of the species (e.g. phosphorylated state, ubiquitinated state, complex component)

Signaling network reconstruction

3. Expand the list of pathways selection

Signaling network reconstruction

3. Expand the list of pathways selection

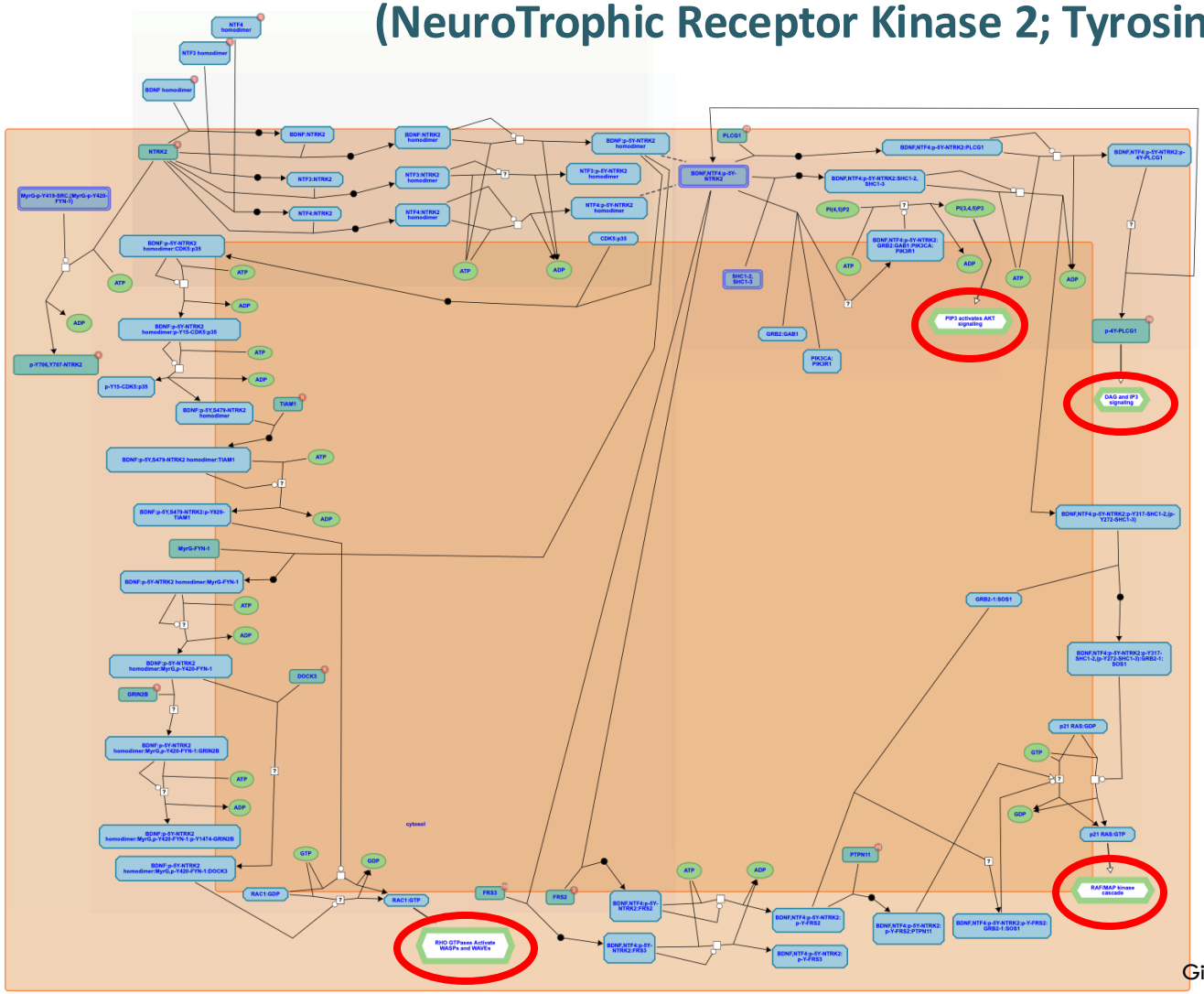


Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

Signaling network reconstruction

3. Expand the list of pathways selection

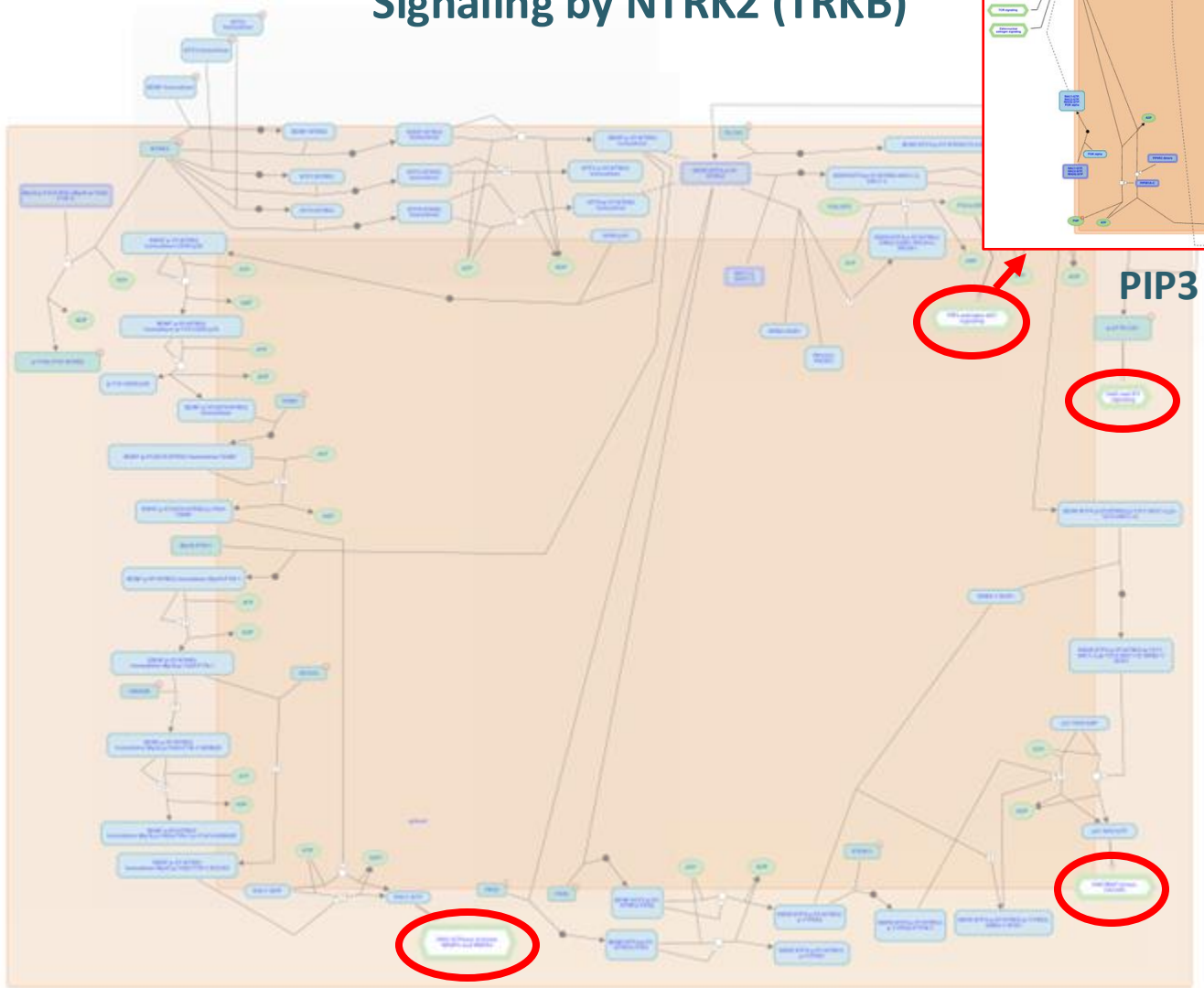
Signaling by NTRK2 (TRKB)
(NeuroTrophic Receptor Kinase 2; Tyrosine Protein Kinase))

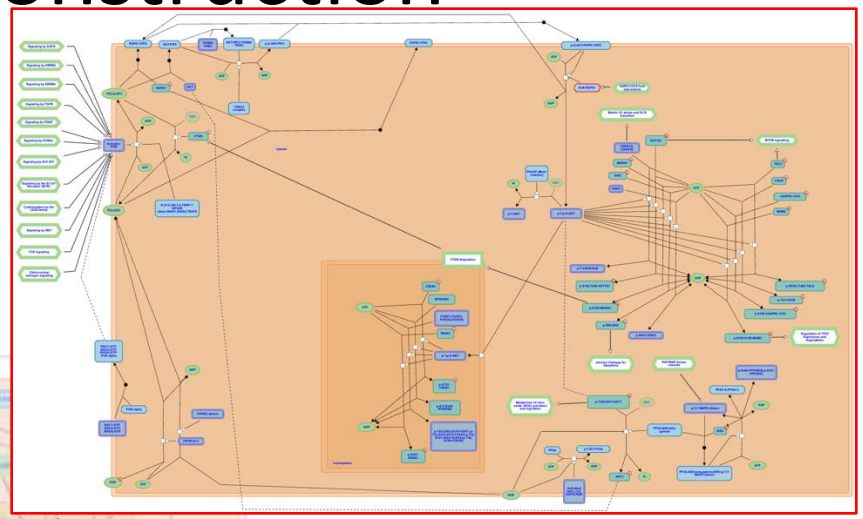


Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

Signaling network reconstruction

3. Expand the list of pathways selection



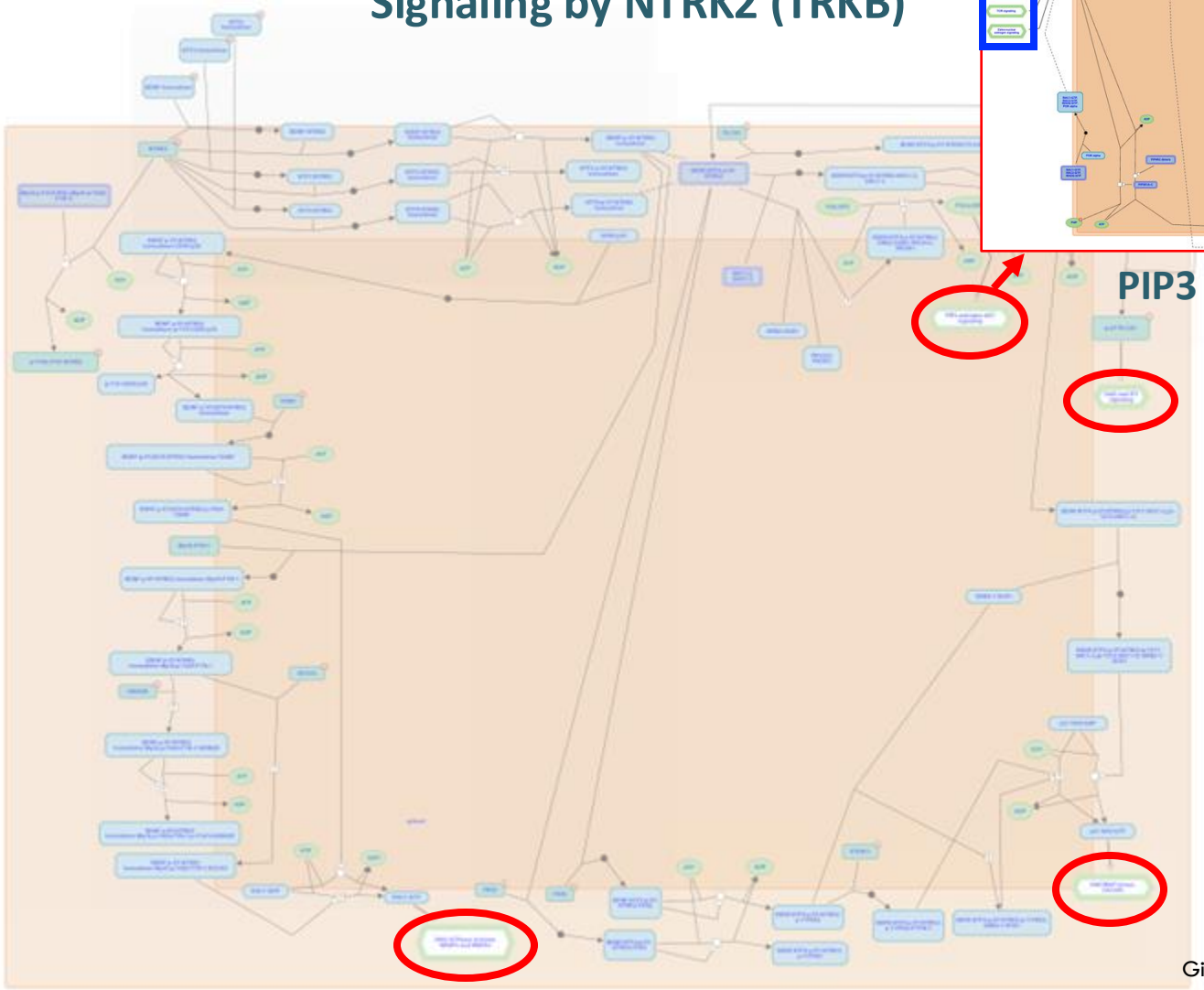


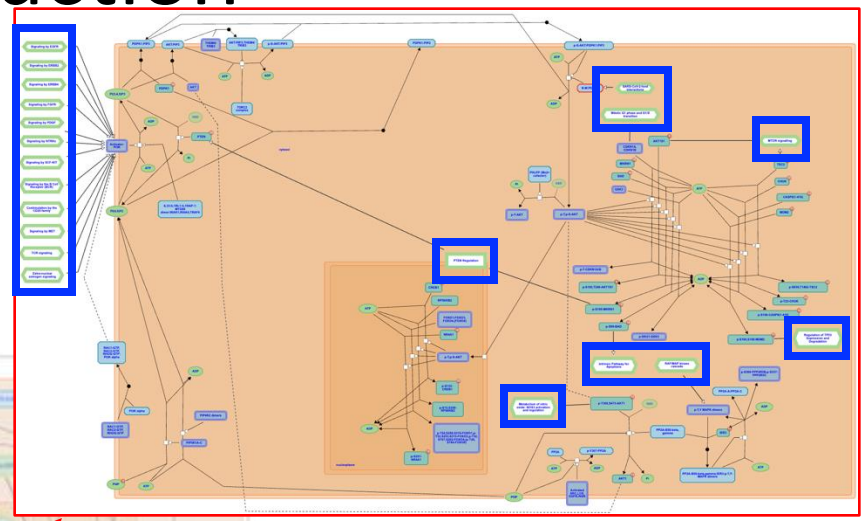
PI3K (phosphatidylinositol 3-kinase) and Akt (protein kinase B)

Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

Signaling network reconstruction

3. Expand the list of pathways selection



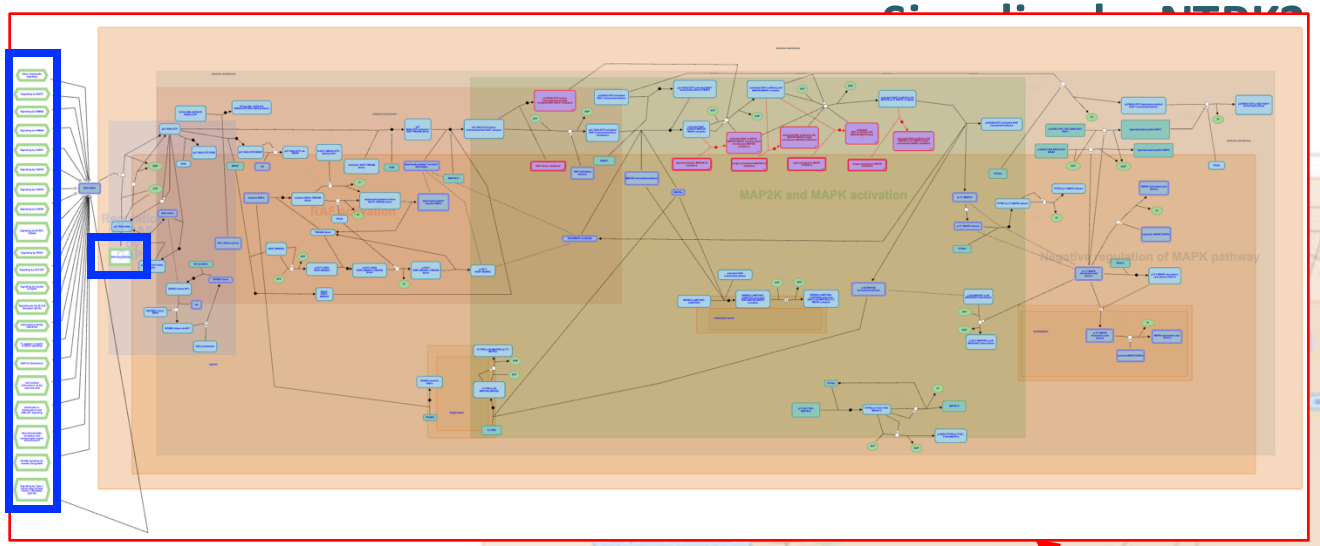


PIP3 activates AKT signaling

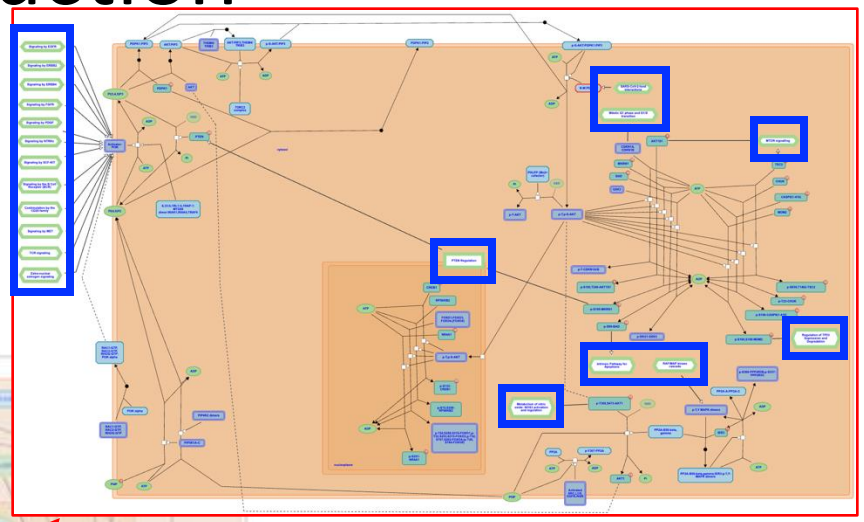
Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

Signaling network reconstruction

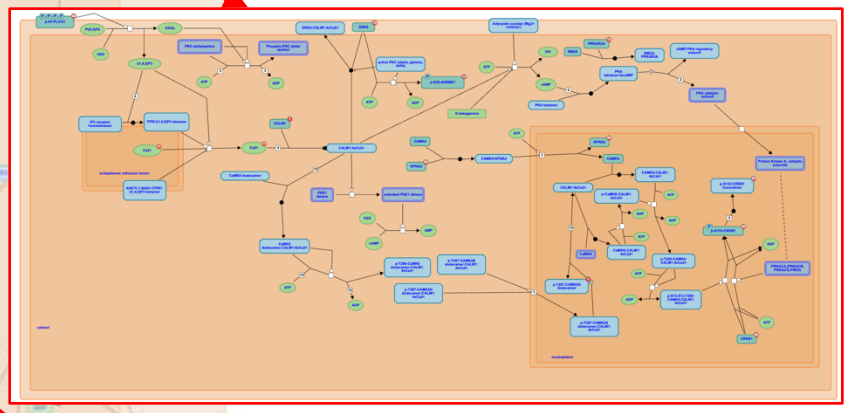
3. Expand the list of pathways selection



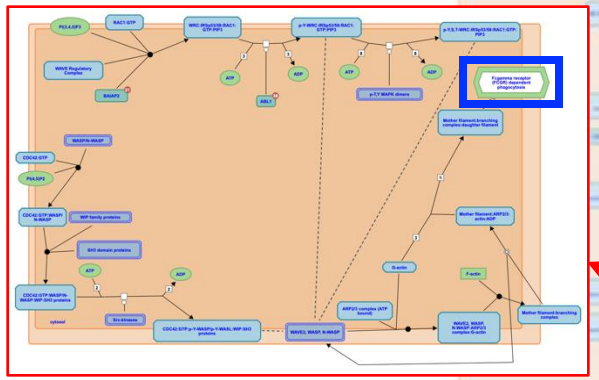
RAF/MAP kinase cascade



PIP3 activates AKT signaling



DAG and IP3 signaling

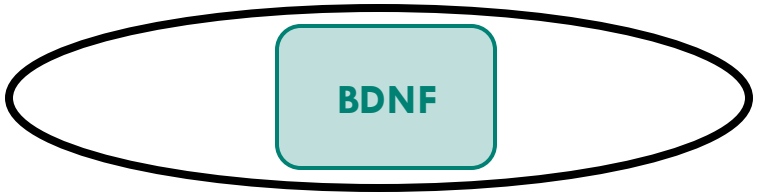


RHO GTPases Activate WASPs and WAVEs

Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

Signaling network reconstruction

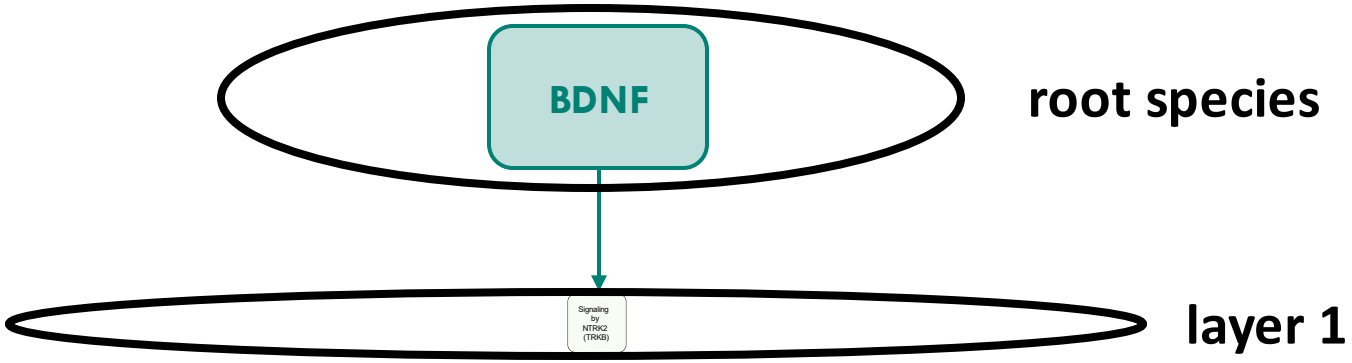
3. Expand the list of pathways selection



root species

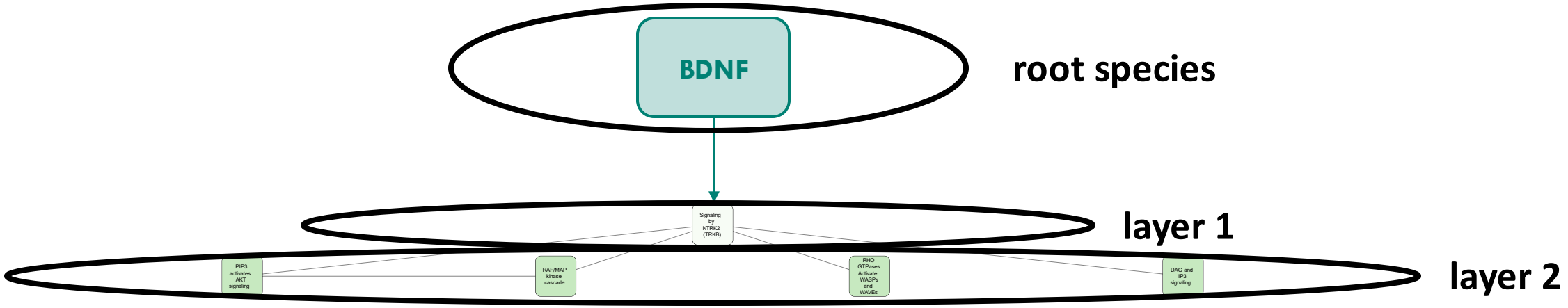
Signaling network reconstruction

3. Expand the list of pathways selection



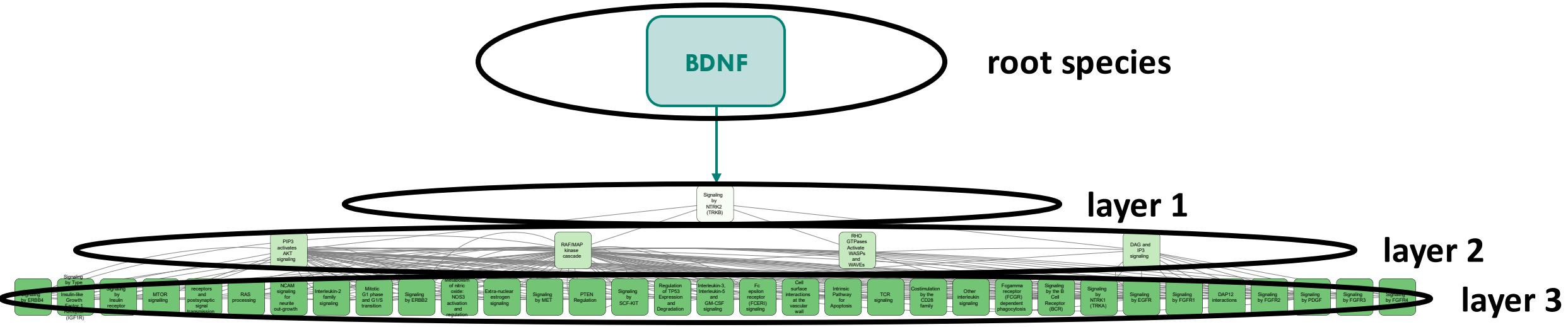
Signaling network reconstruction

3. Expand the list of pathways selection



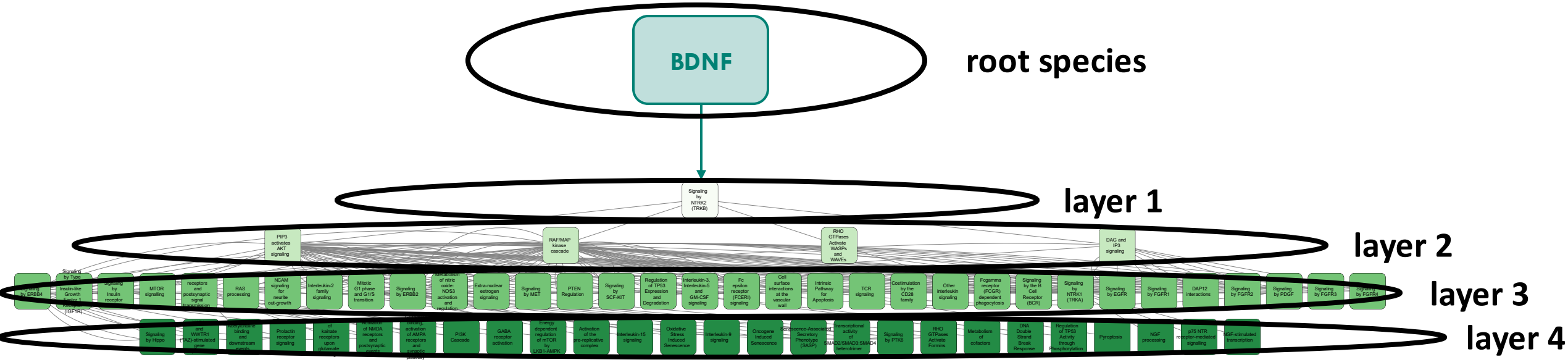
Signaling network reconstruction

3. Expand the list of pathways selection



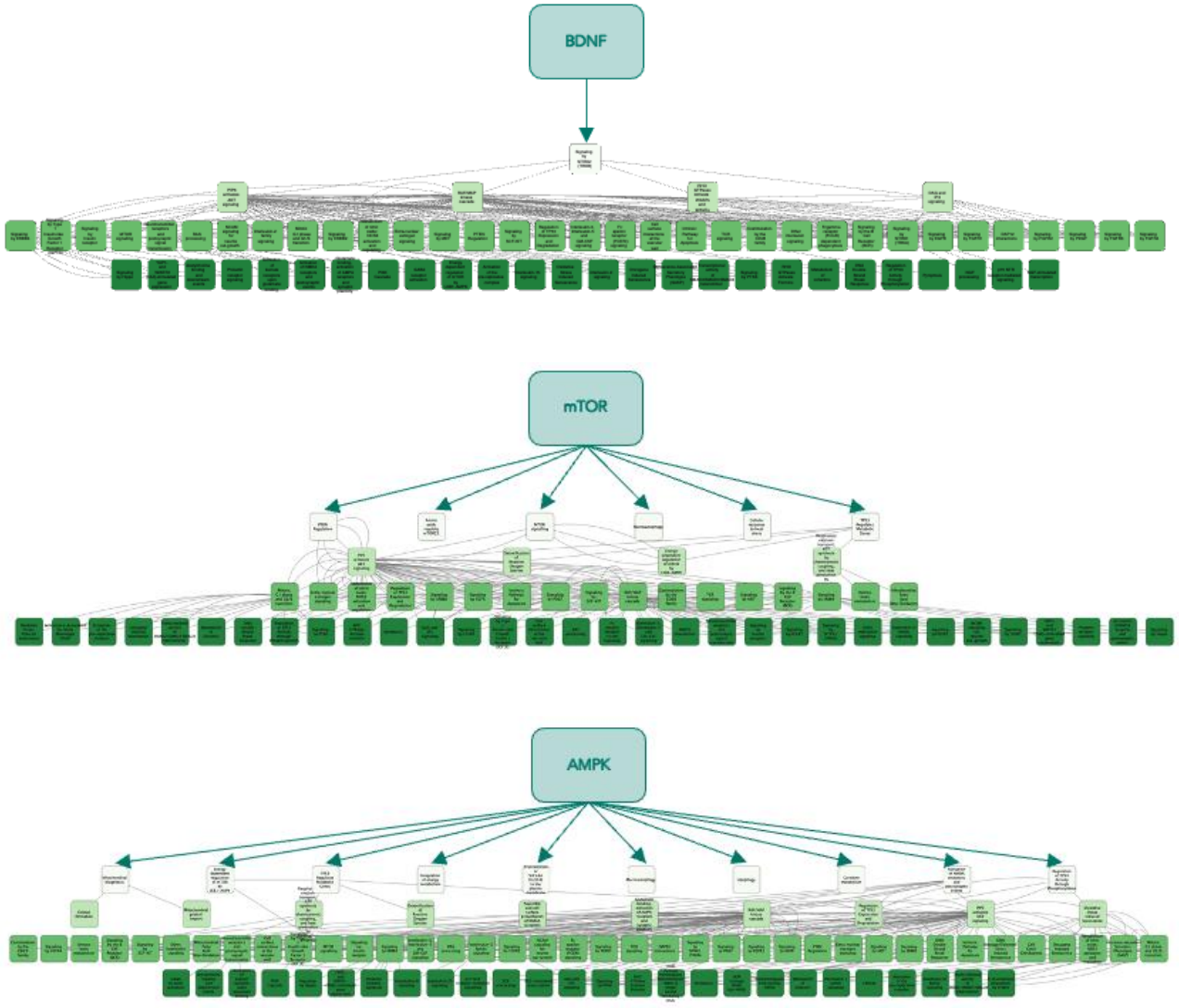
Signaling network reconstruction

3. Expand the list of pathways selection



Signaling network reconstruction

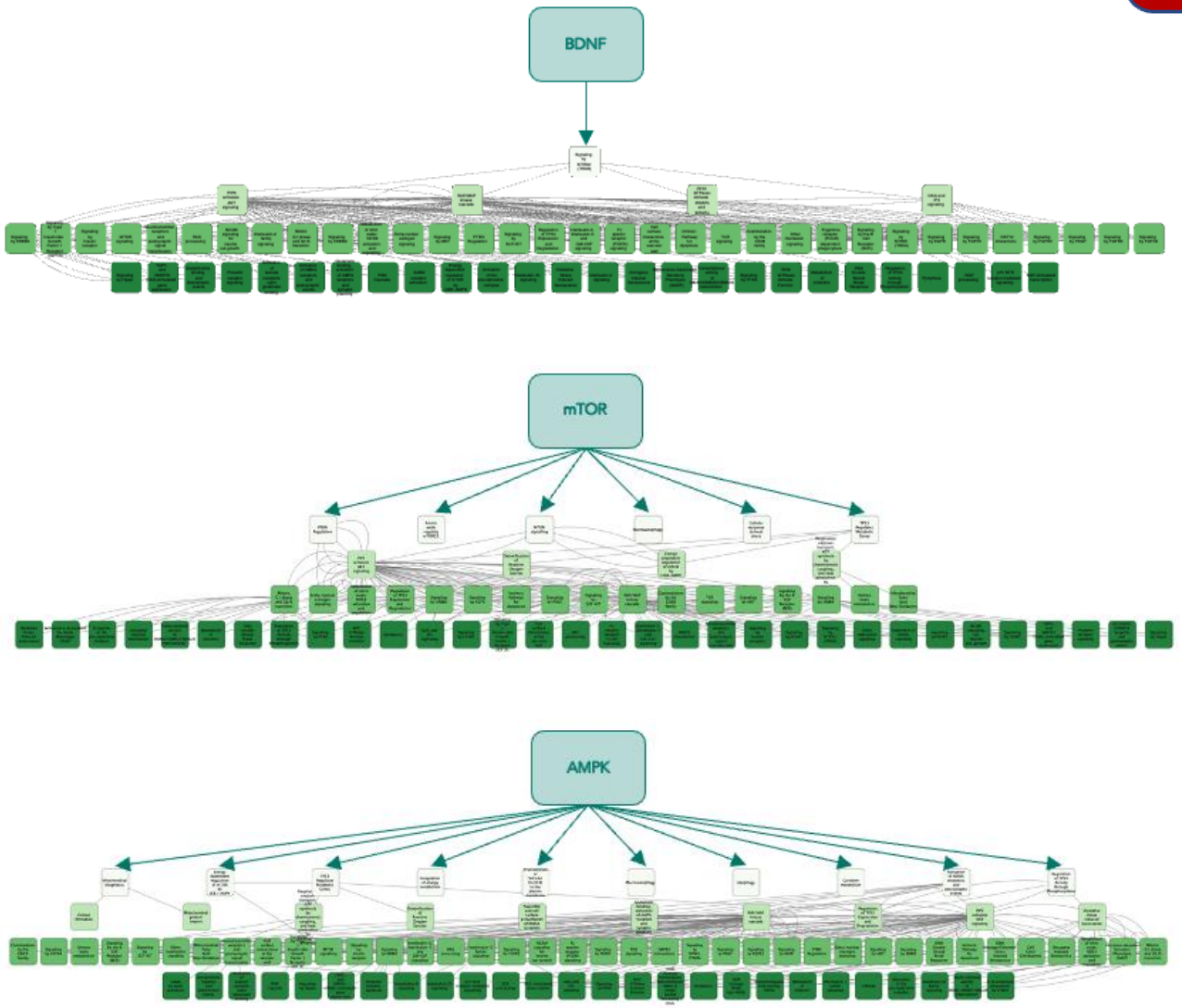
3. Expand the list of pathways selection



Signaling network reconstruction

3. Expand the list of pathways selection

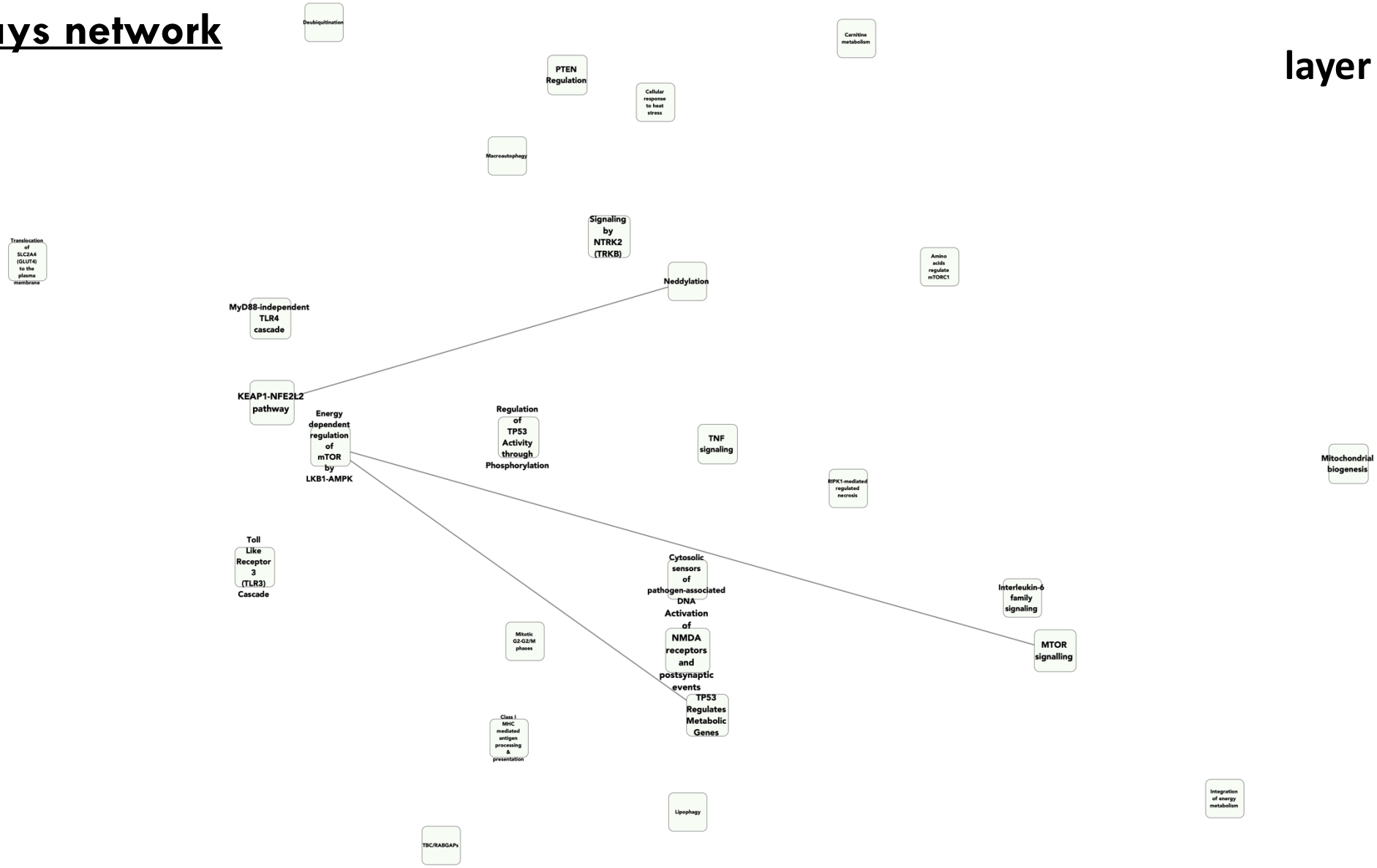
115 Pathways



Signaling network reconstruction

Final pathways network

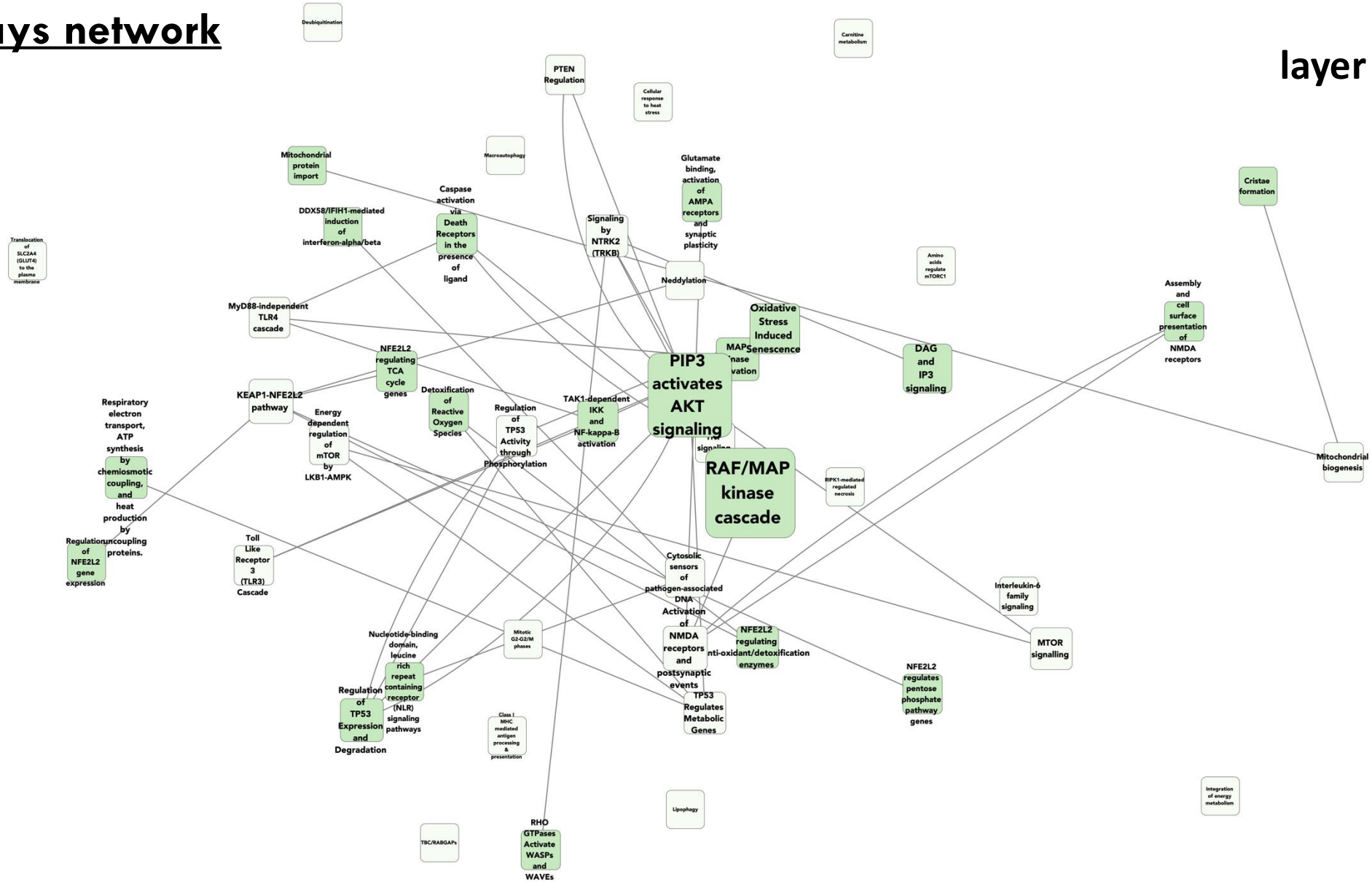
layer 1



Signaling network reconstruction

Final pathways network

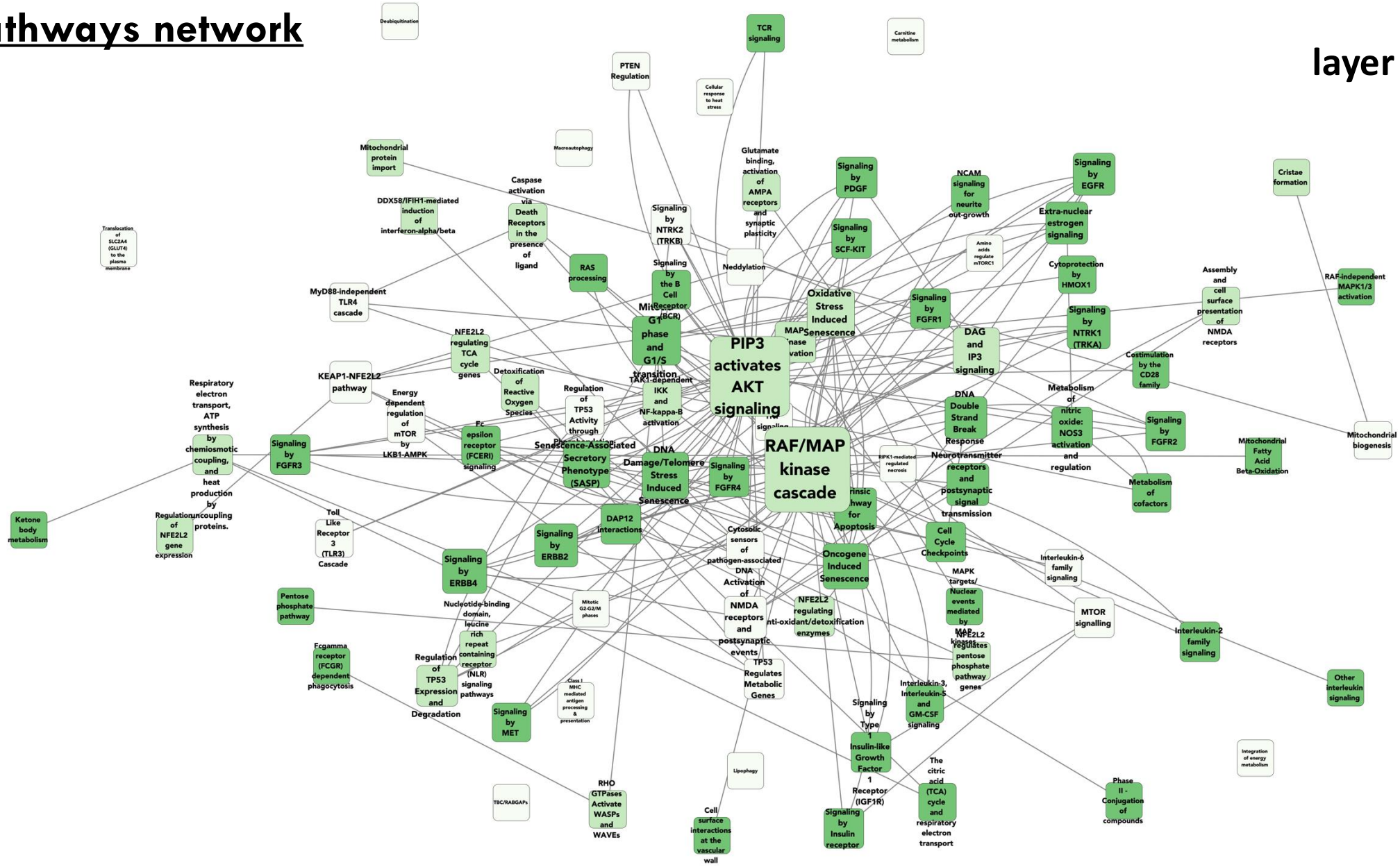
layer 2



Signaling network reconstruction

Final pathways network

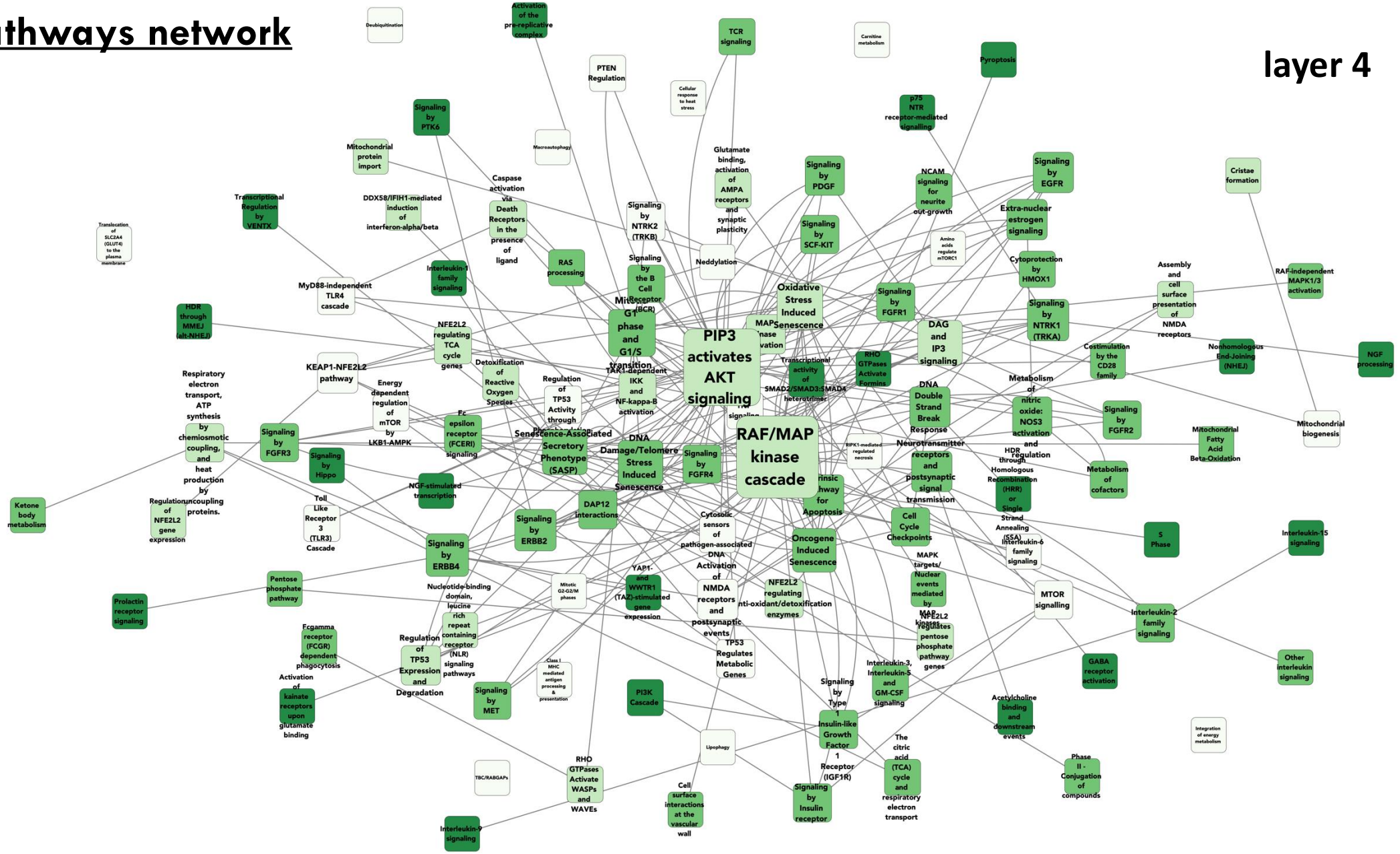
layer 3



Signaling network reconstruction

Final pathways network

layer 4

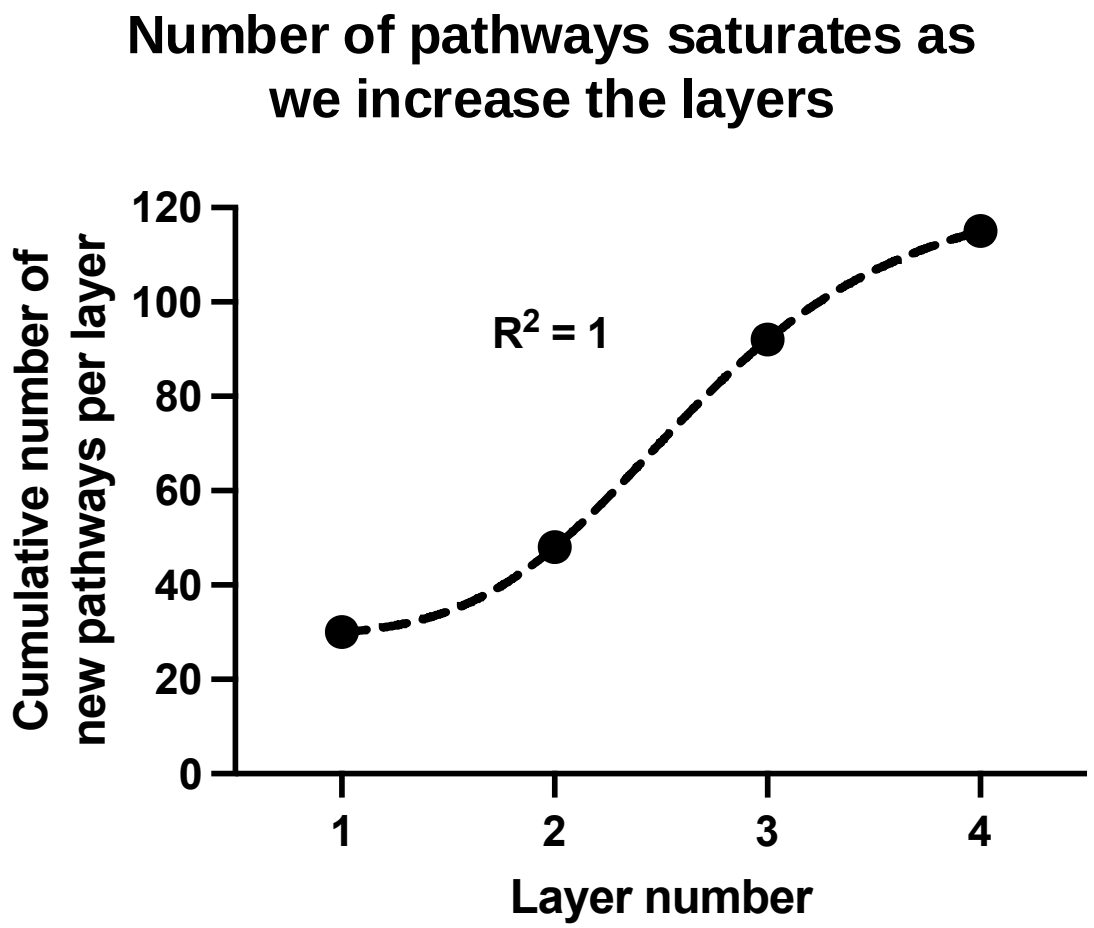


Signaling network reconstruction

Are 4 layers sufficient?

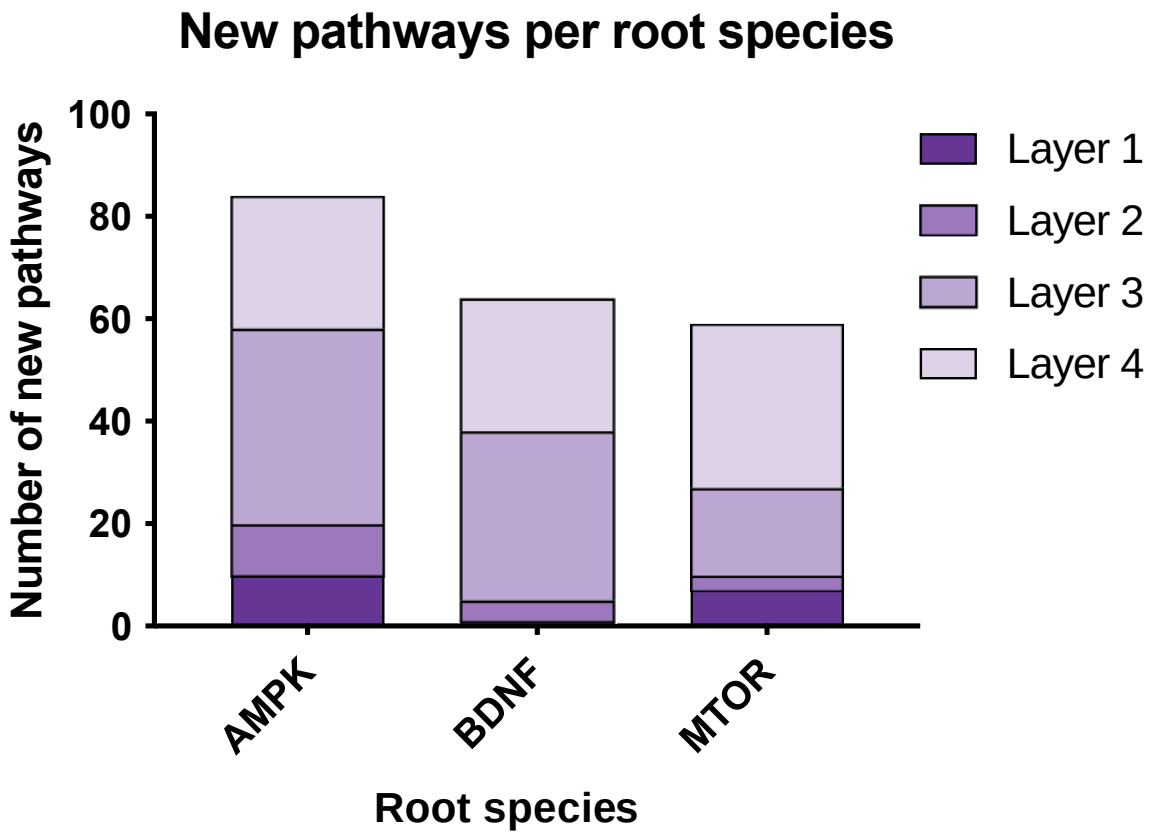
Signaling network reconstruction

3. Expand the list of pathways selection



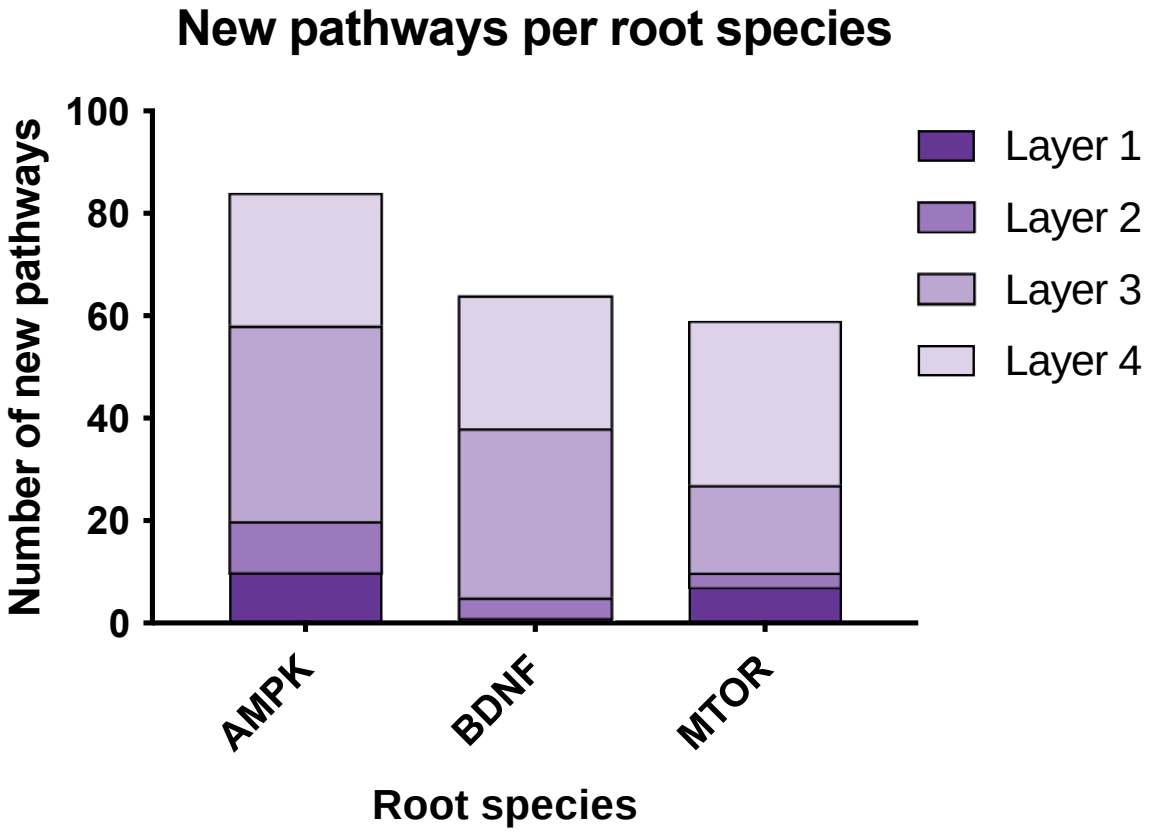
Signaling network reconstruction

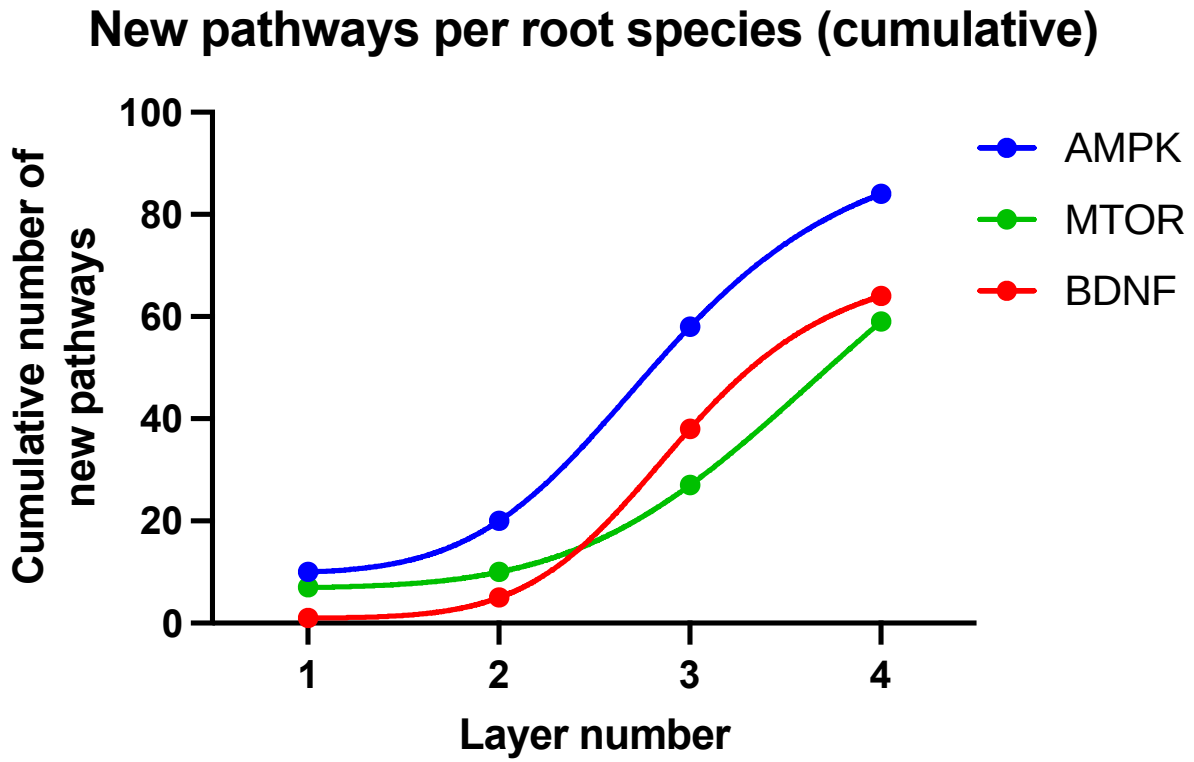
3. Expand the list of pathways selection



Signaling network reconstruction

3. Expand the list of pathways selection





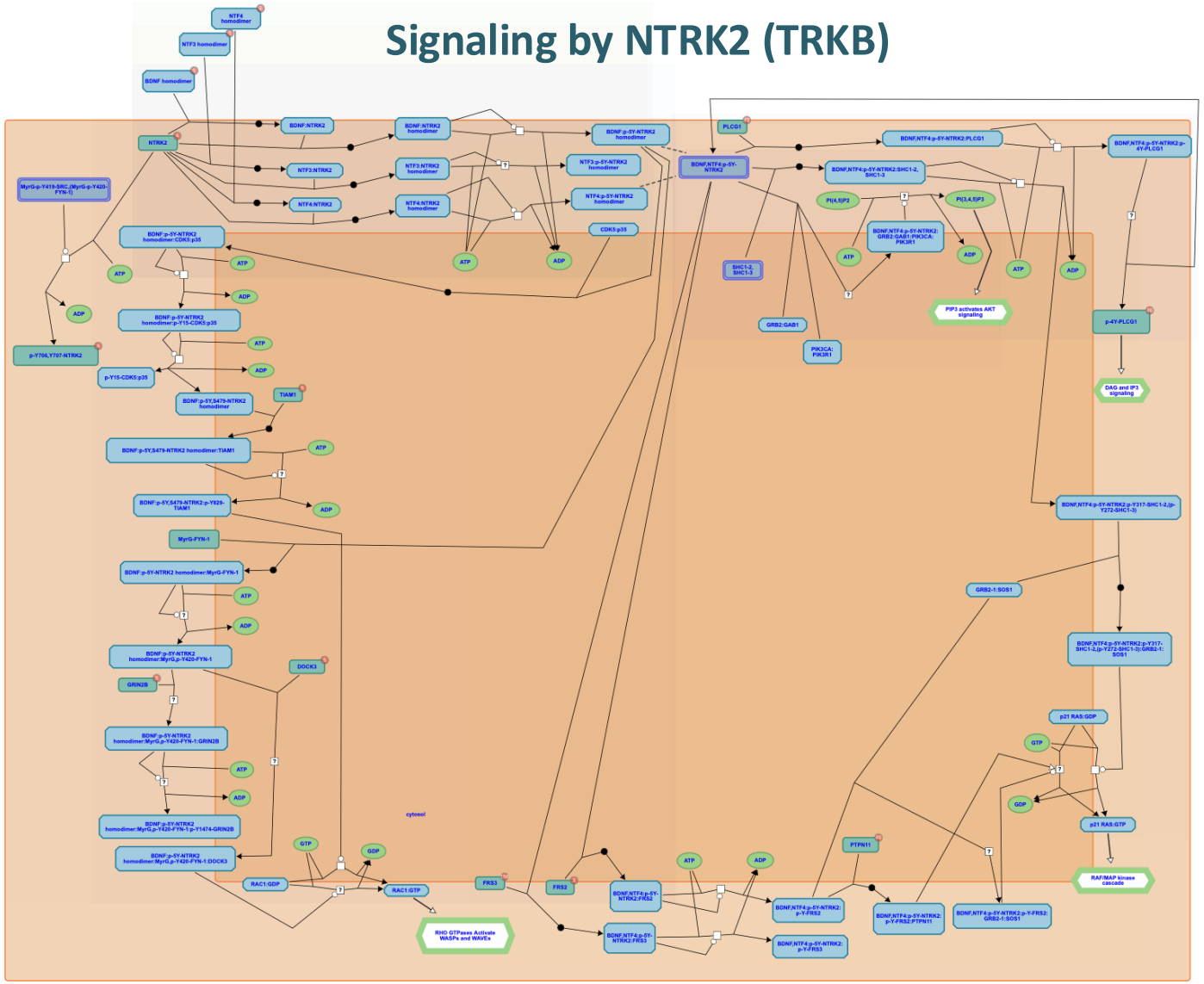
Signaling network reconstruction

4. Curate manually all the pathways of the final list

Signaling network reconstruction

4. Curate manually all the pathways of the final list

Reactions and species information can be downloaded automatically but:



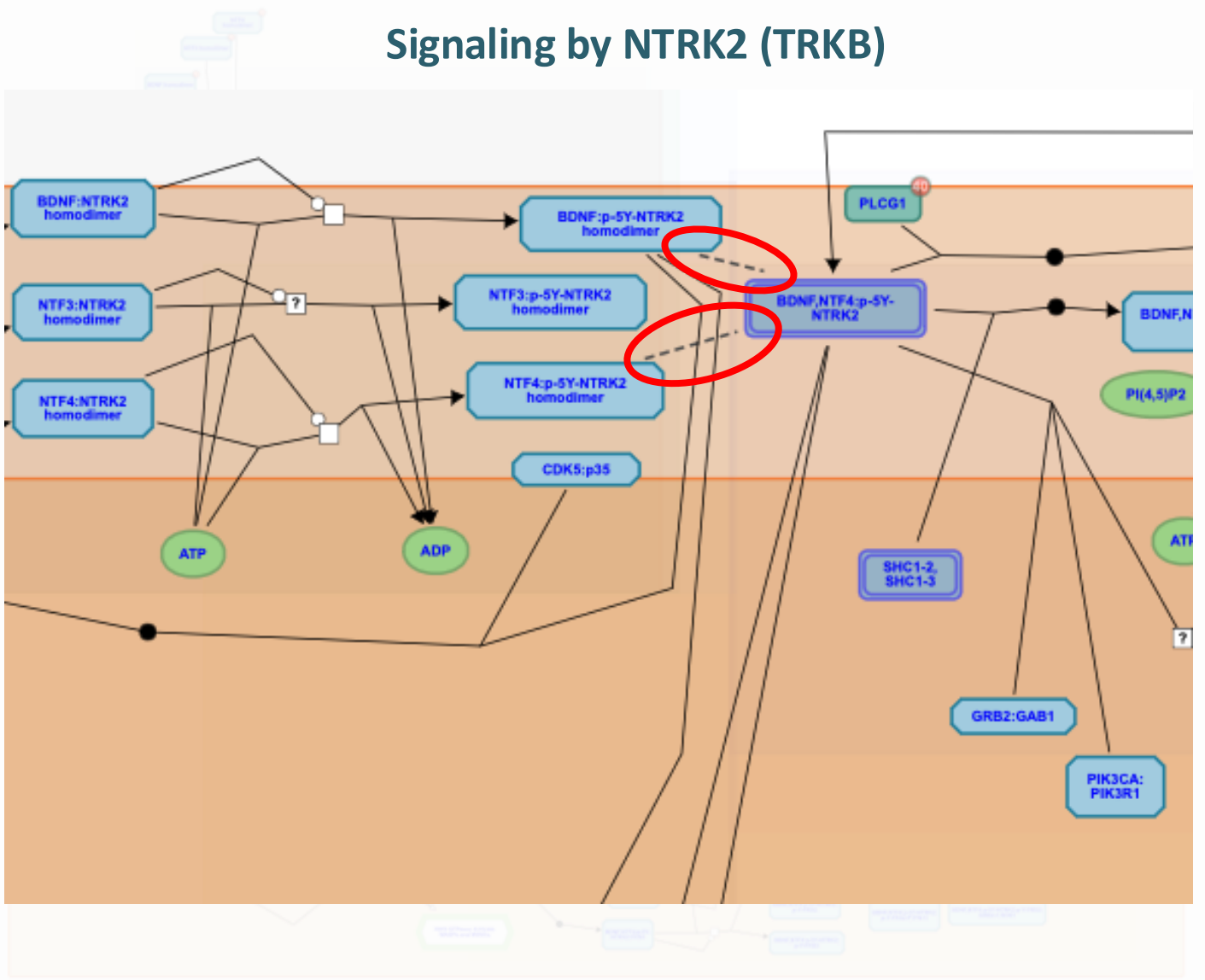
Gillespie M., et al. “The Reactome Pathway Knowledgebase 2022.” *Nucleic Acids Research*, 2022

Signaling network reconstruction

4. Curate manually all the pathways of the final list

Reactions and species information can be downloaded automatically but:

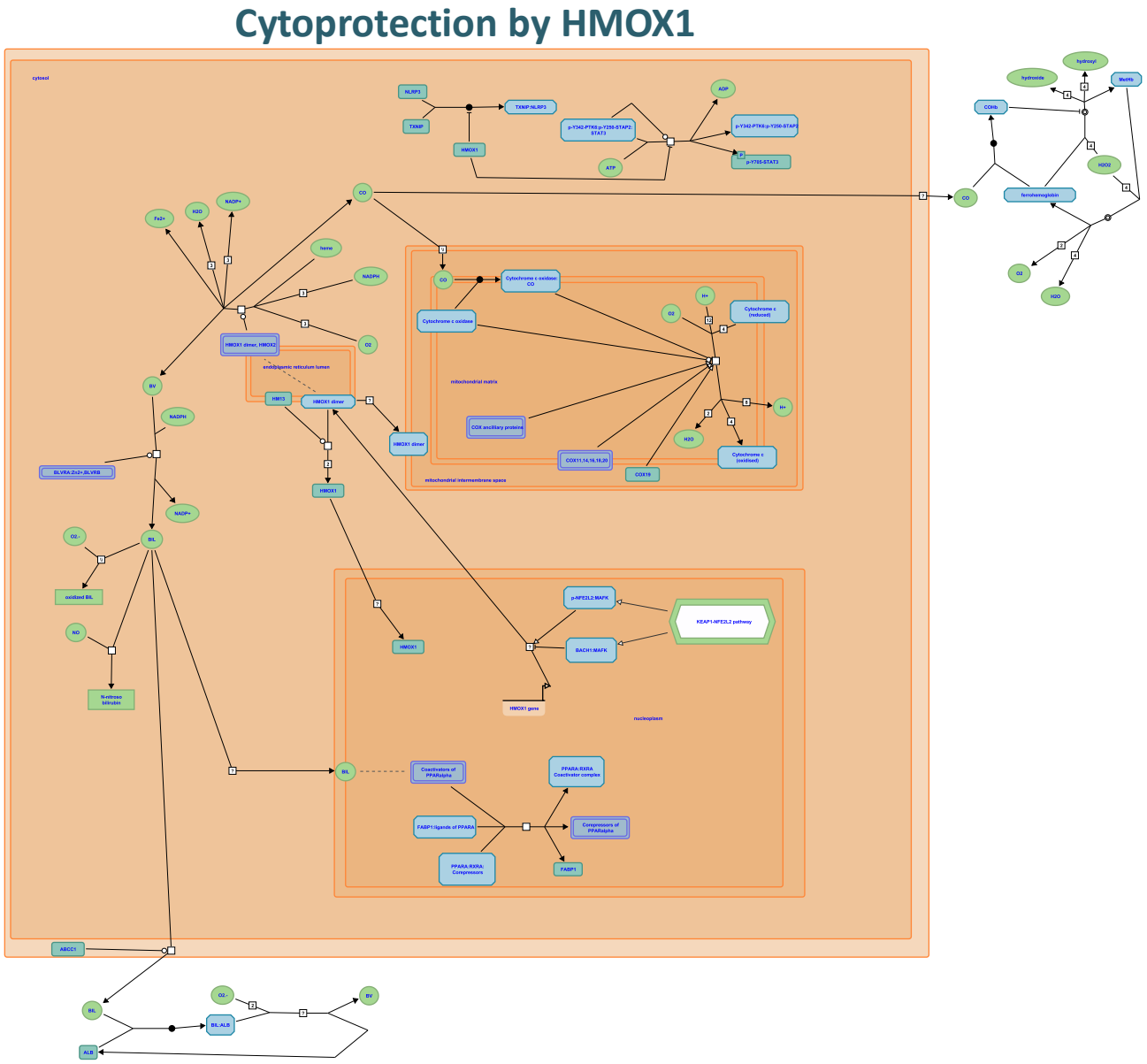
1) **Dashed lines in the graph represent flow of information but the data does not exist.**



Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

Signaling network reconstruction

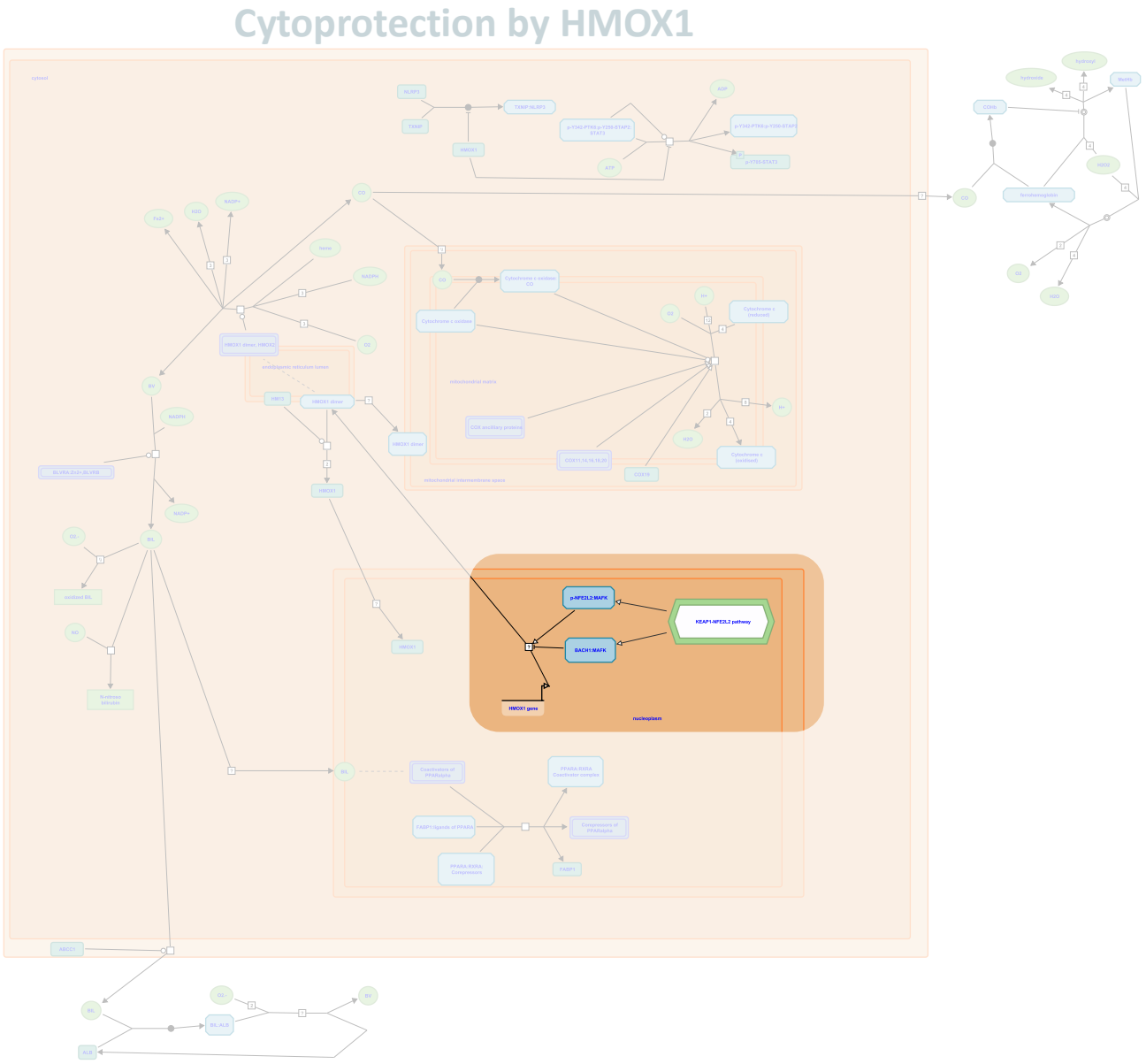
4. Curate manually all the pathways of the final list



Gillespie M., et al. “The Reactome Pathway Knowledgebase 2022.” *Nucleic Acids Research*, 2022

Signaling network reconstruction

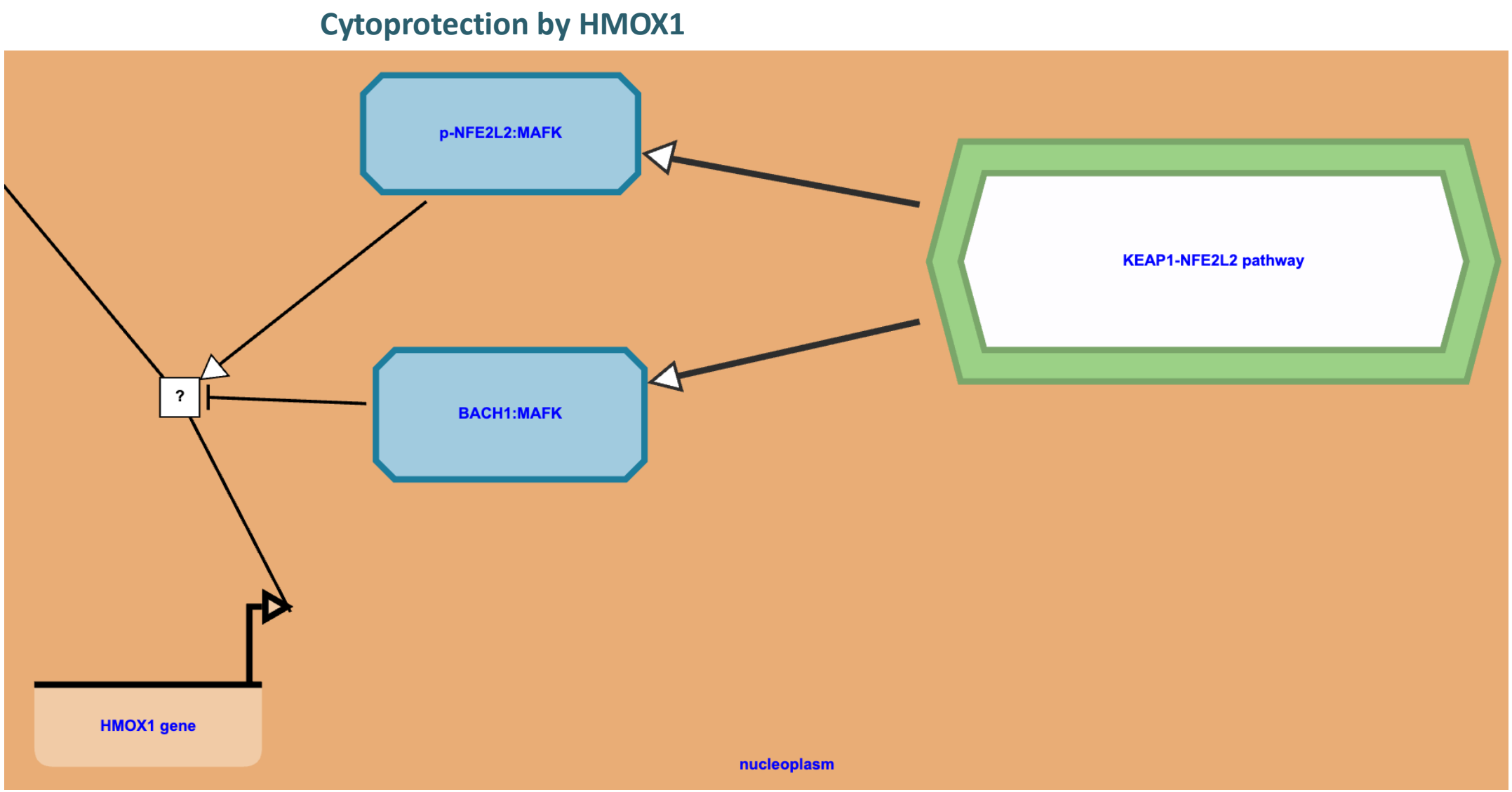
4. Curate manually all the pathways of the final list



Gillespie M., et al. “The Reactome Pathway Knowledgebase 2022.” *Nucleic Acids Research*, 2022

Signaling network reconstruction

4. Curate manually all the pathways of the final list

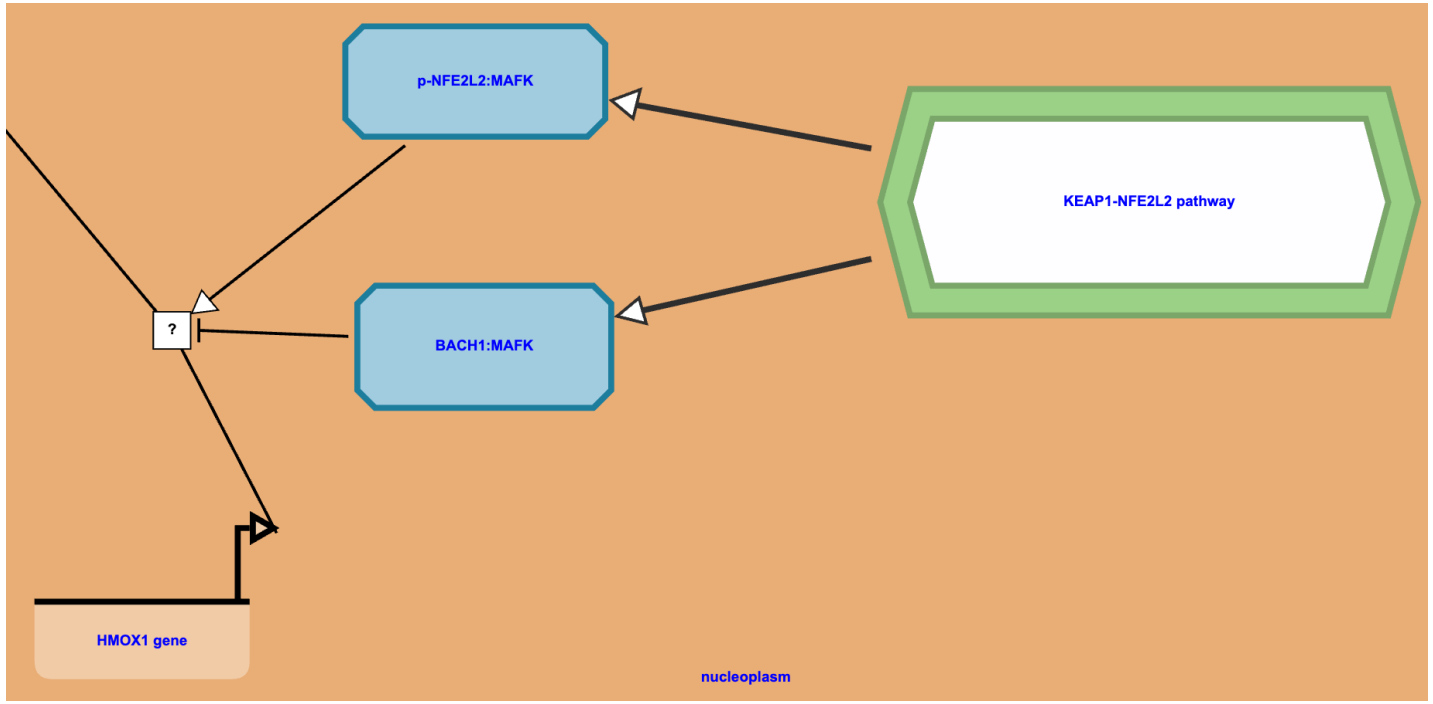


Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

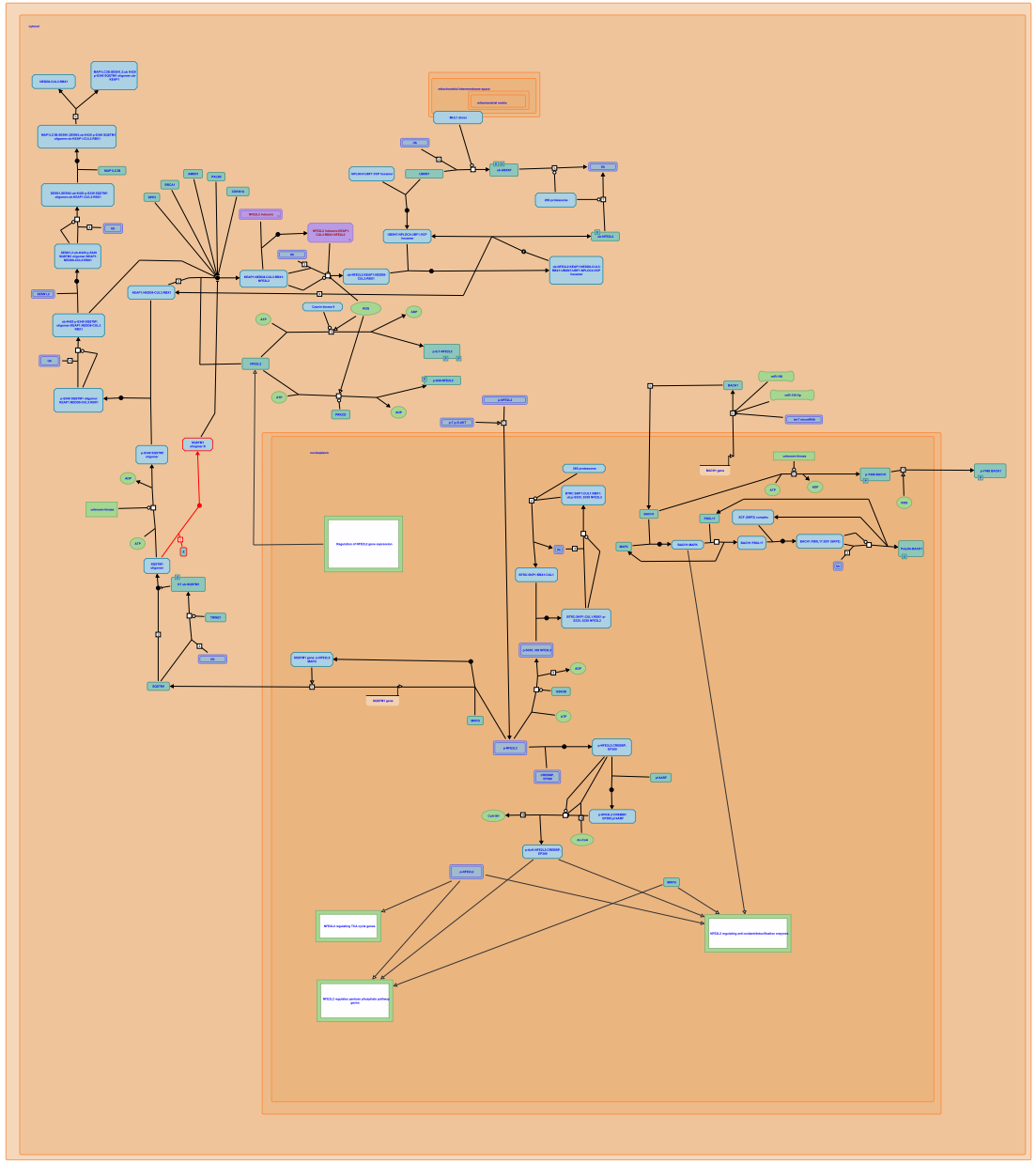
Signaling network reconstruction

4. Curate manually all the pathways of the final list

Cytoprotection by HMOX1



KEAP1-NFE2L2 pathway

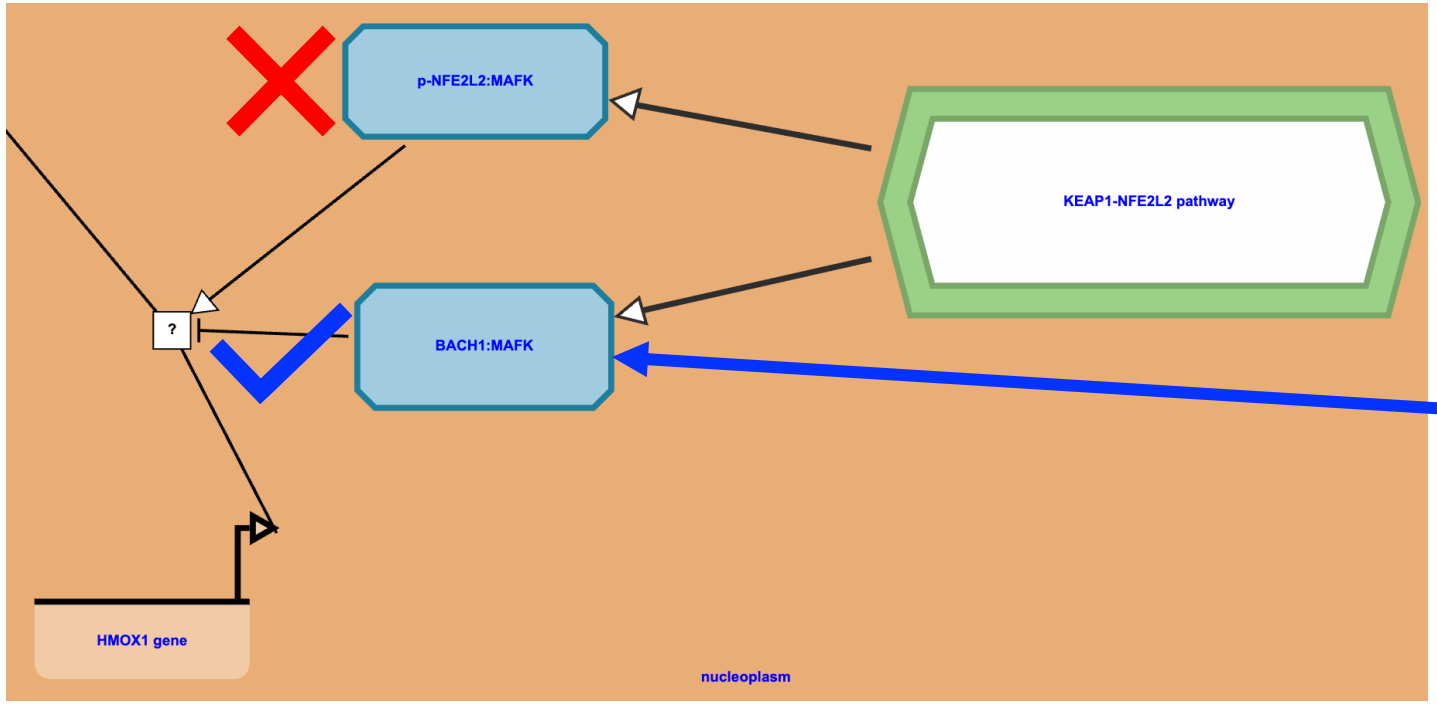


Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

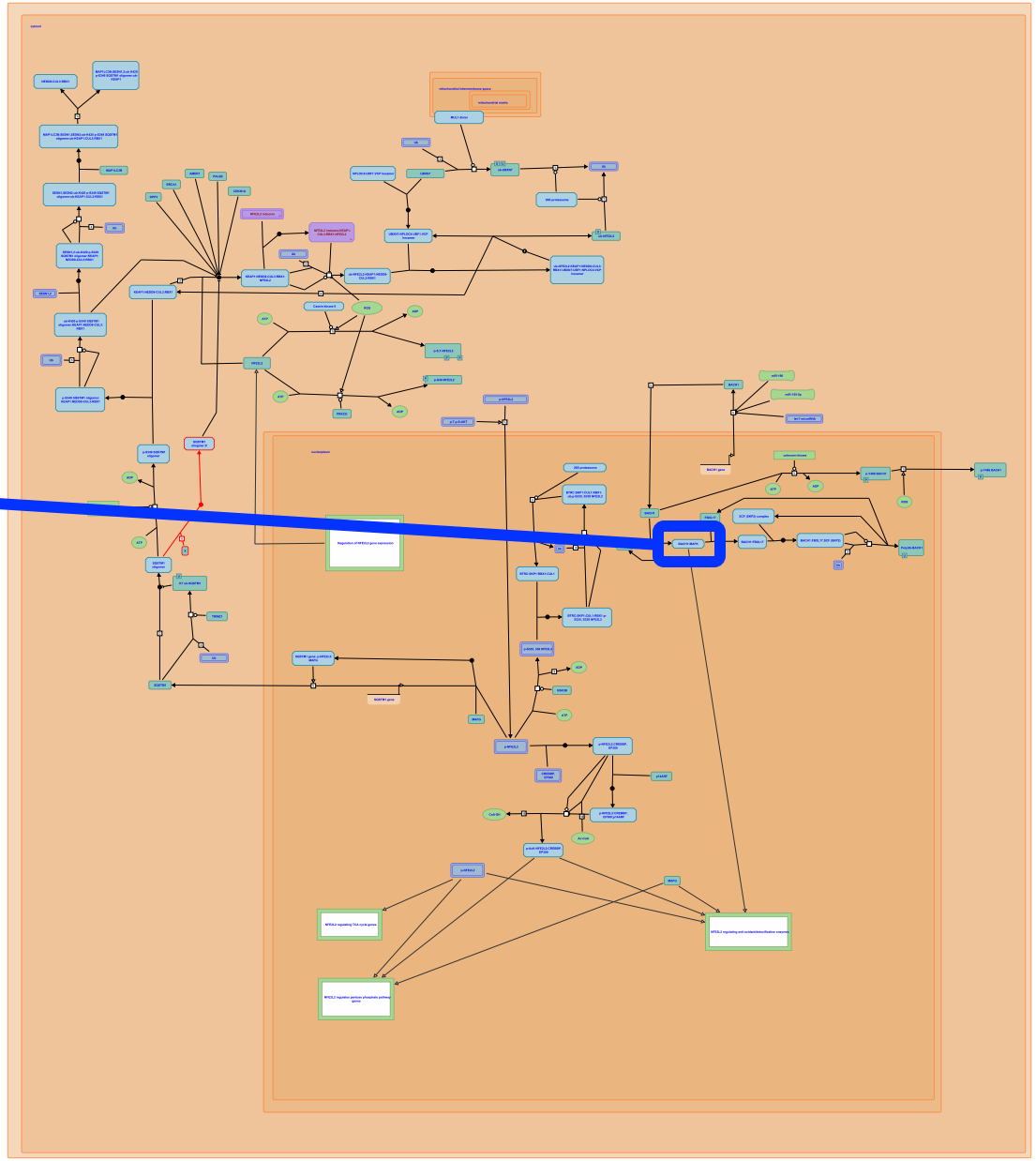
Signaling network reconstruction

4. Curate manually all the pathways of the final list

Cytoprotection by HMOX1



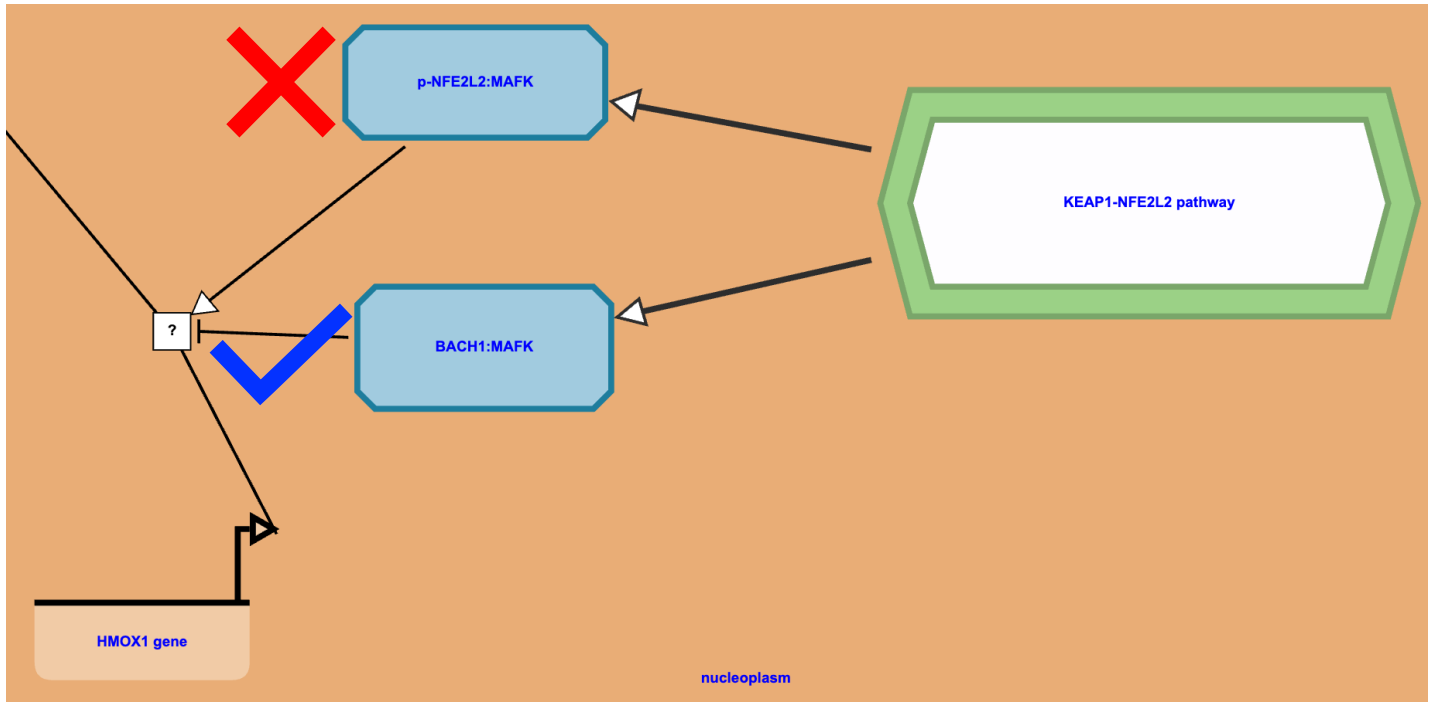
KEAP1-NFE2L2 pathway

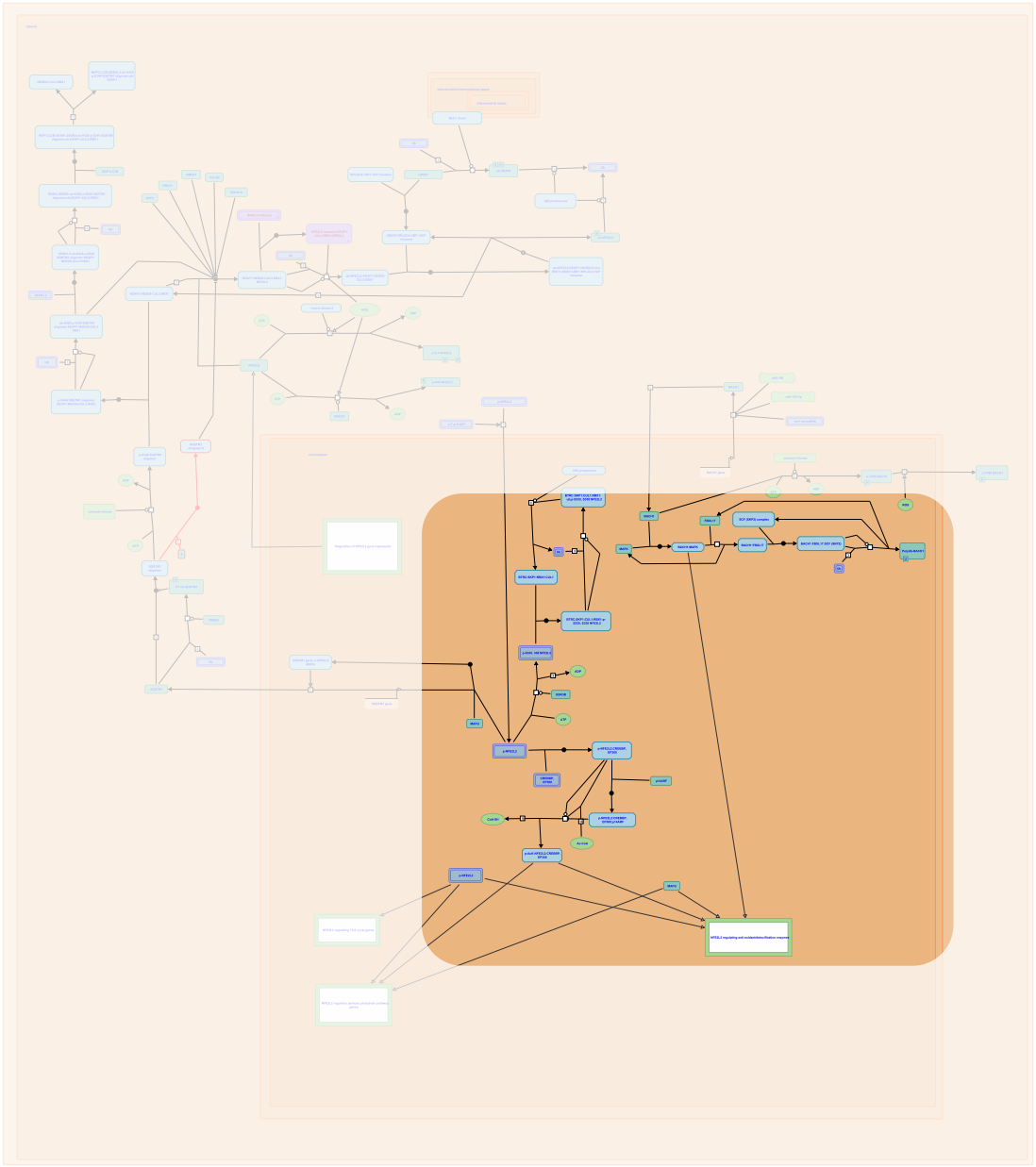


Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

Signaling network reconstruction

4. Curate manually all the pathways of the final list



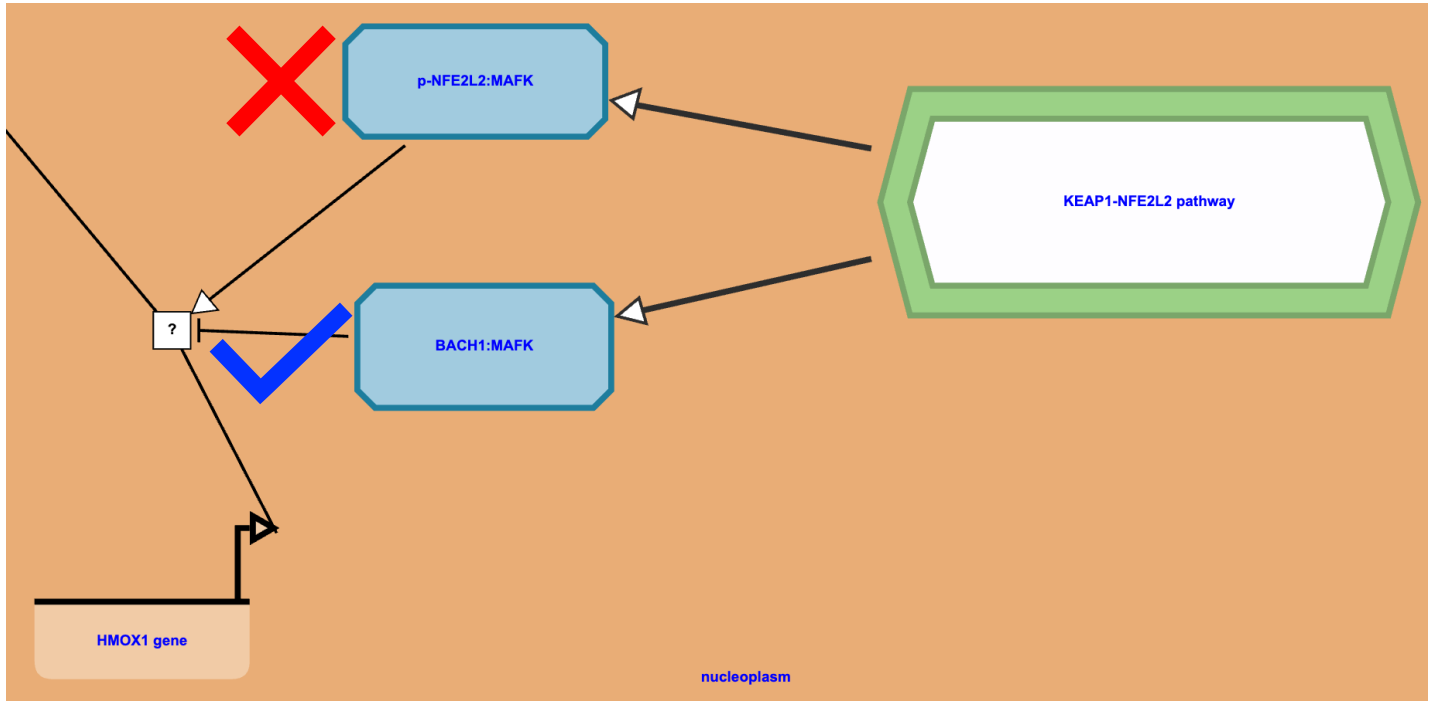


Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

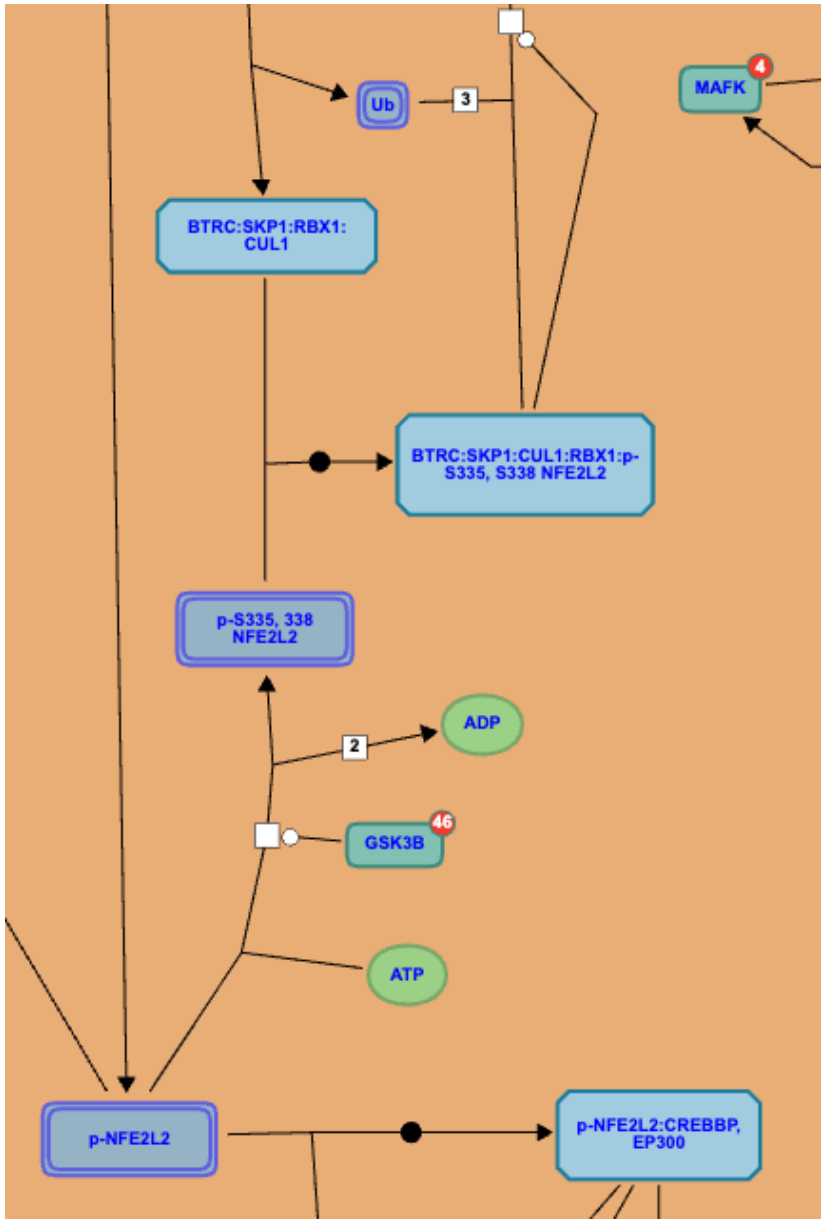
Signaling network reconstruction

4. Curate manually all the pathways of the final list

Cytoprotection by HMOX1



KEAP1-NFE2L2 pathway

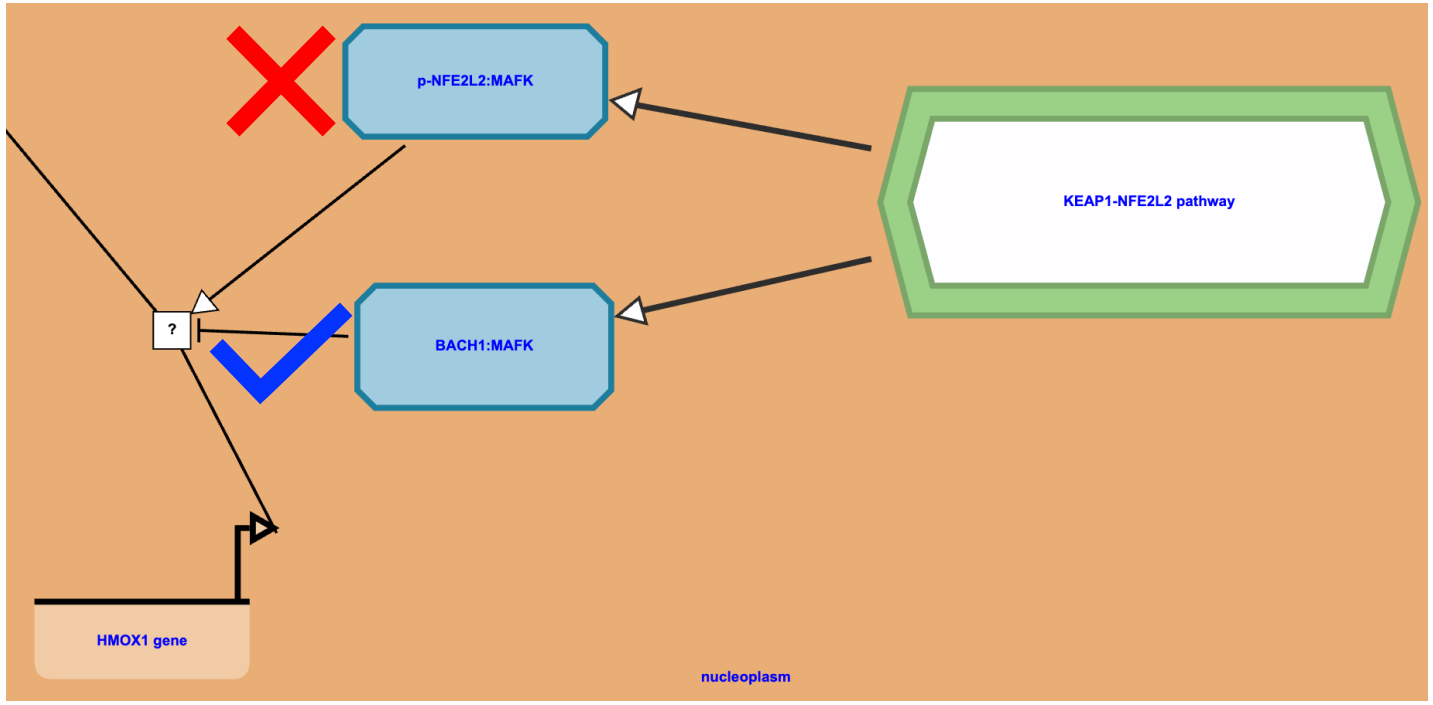


Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

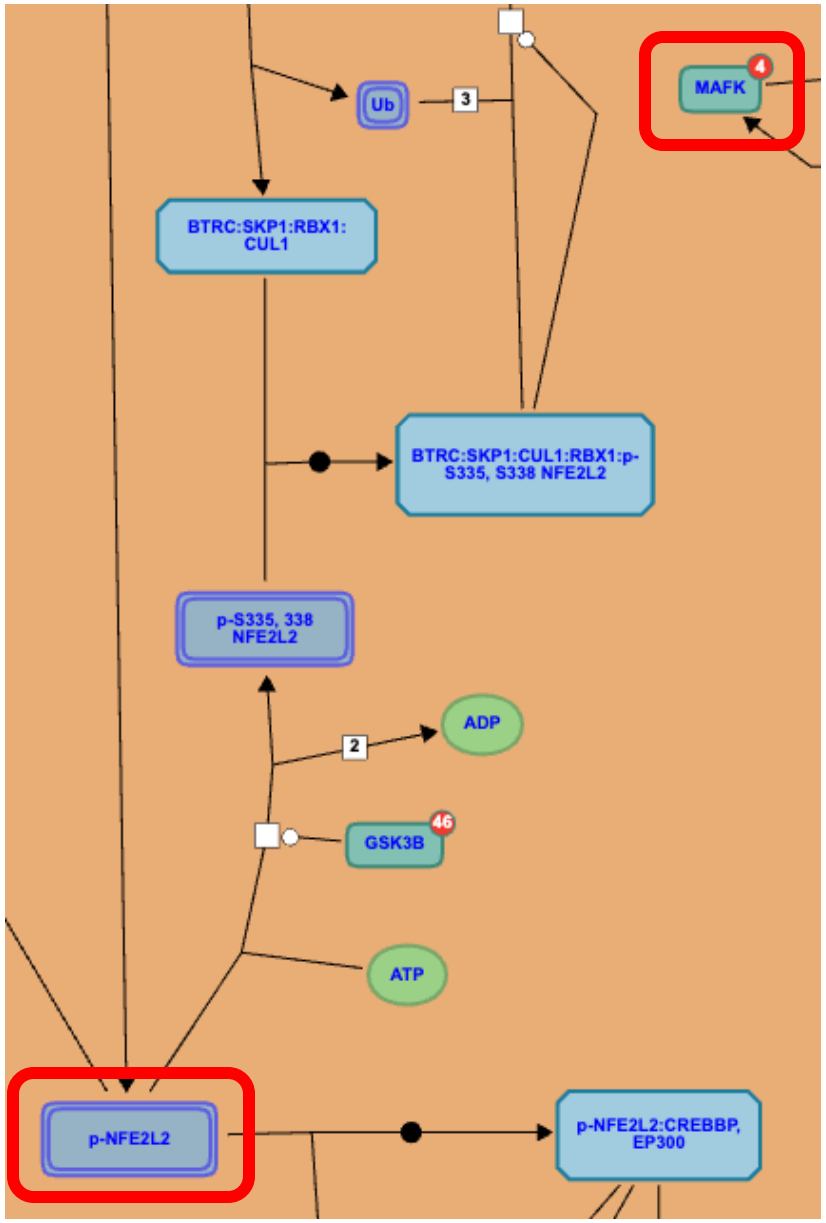
Signaling network reconstruction

4. Curate manually all the pathways of the final list

Cytoprotection by HMOX1



KEAP1-NFE2L2 pathway

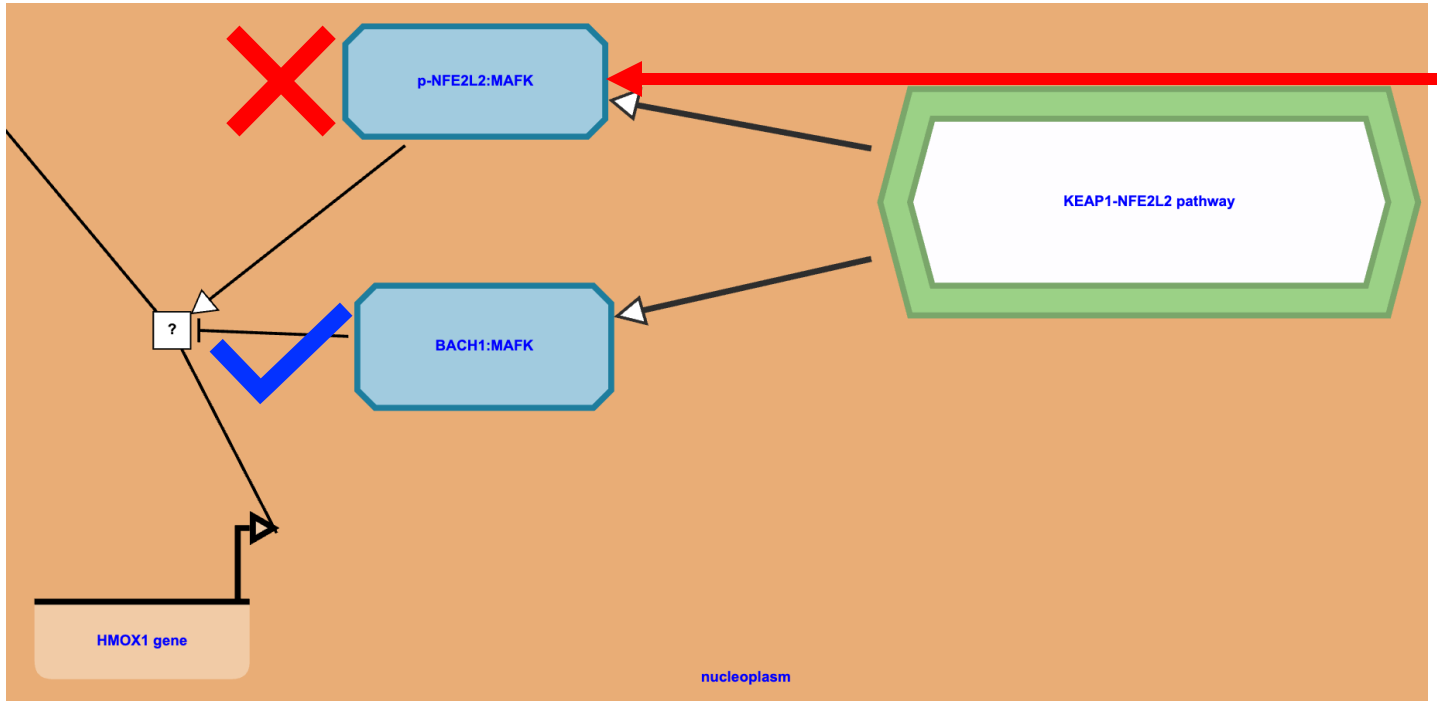


Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

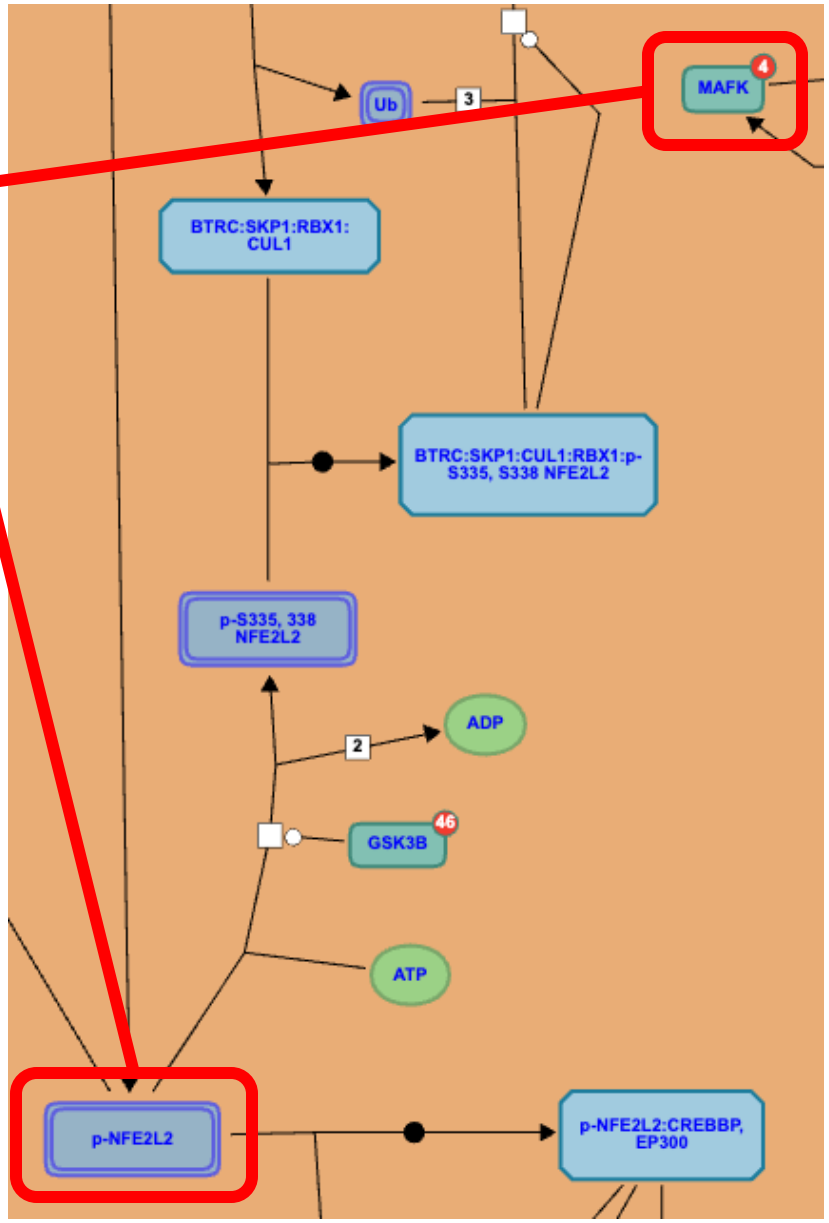
Signaling network reconstruction

4. Curate manually all the pathways of the final list

Cytoprotection by HMOX1



KEAP1-NFE2L2 pathway



Create a reaction:

p-NFE2L2 + MAFK → p-NFE2L2:MAFK

Gillespie M., et al. "The Reactome Pathway Knowledgebase 2022." *Nucleic Acids Research*, 2022

Signaling network reconstruction

4. Curate manually all the pathways of the final list

Reactions and species information can be downloaded automatically but:

1) **Dashed lines in the graph represent flow of information but the data does not exist.**

2) **The connection between different pathways should be checked.**

Signaling network reconstruction

4. Curate manually all the pathways of the final list

Reactions and species information can be downloaded automatically but:

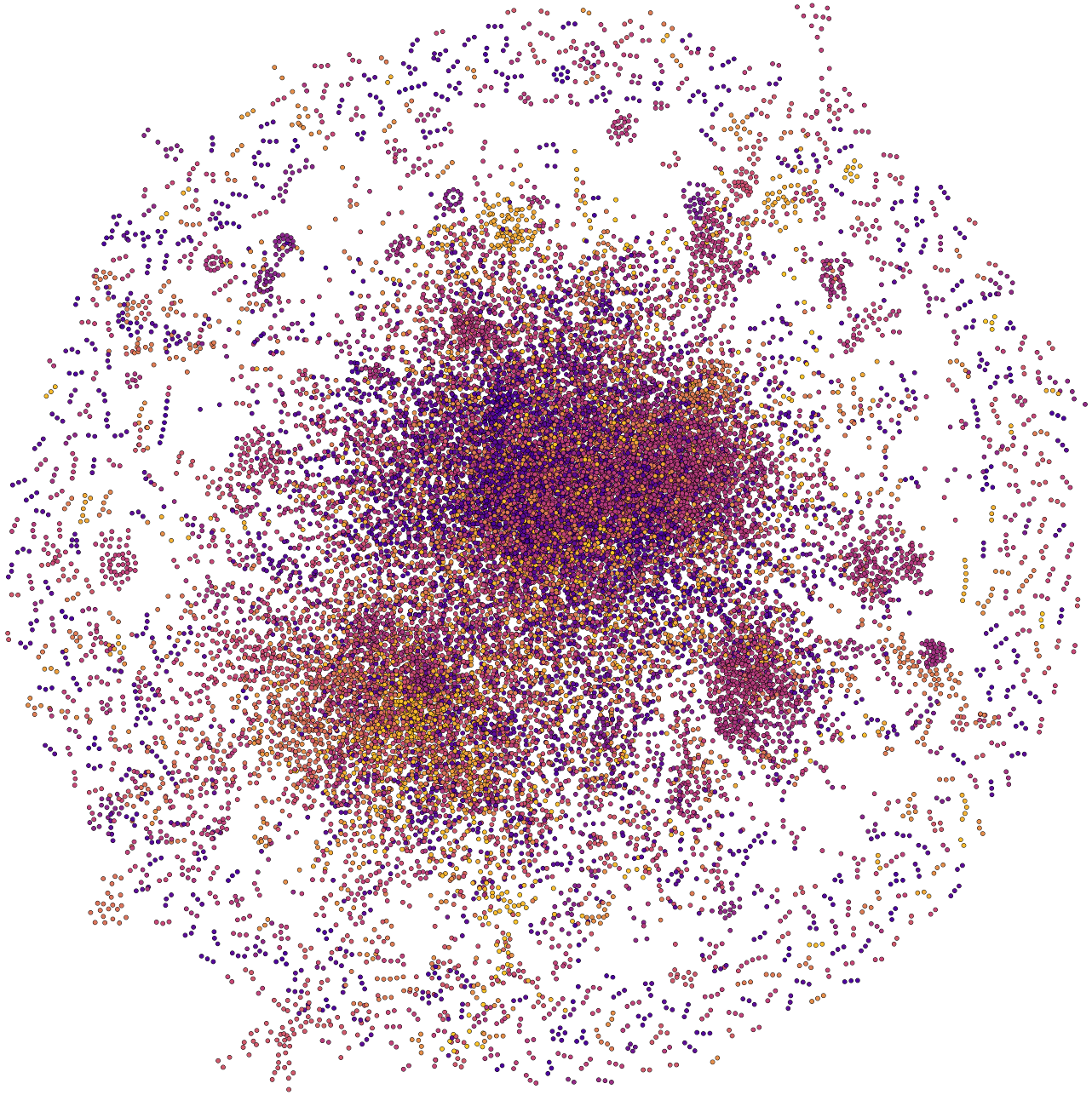
1) **Dashed lines in the graph represent flow of information but the data does not exist.**

2) **The connection between different pathways should be checked.**

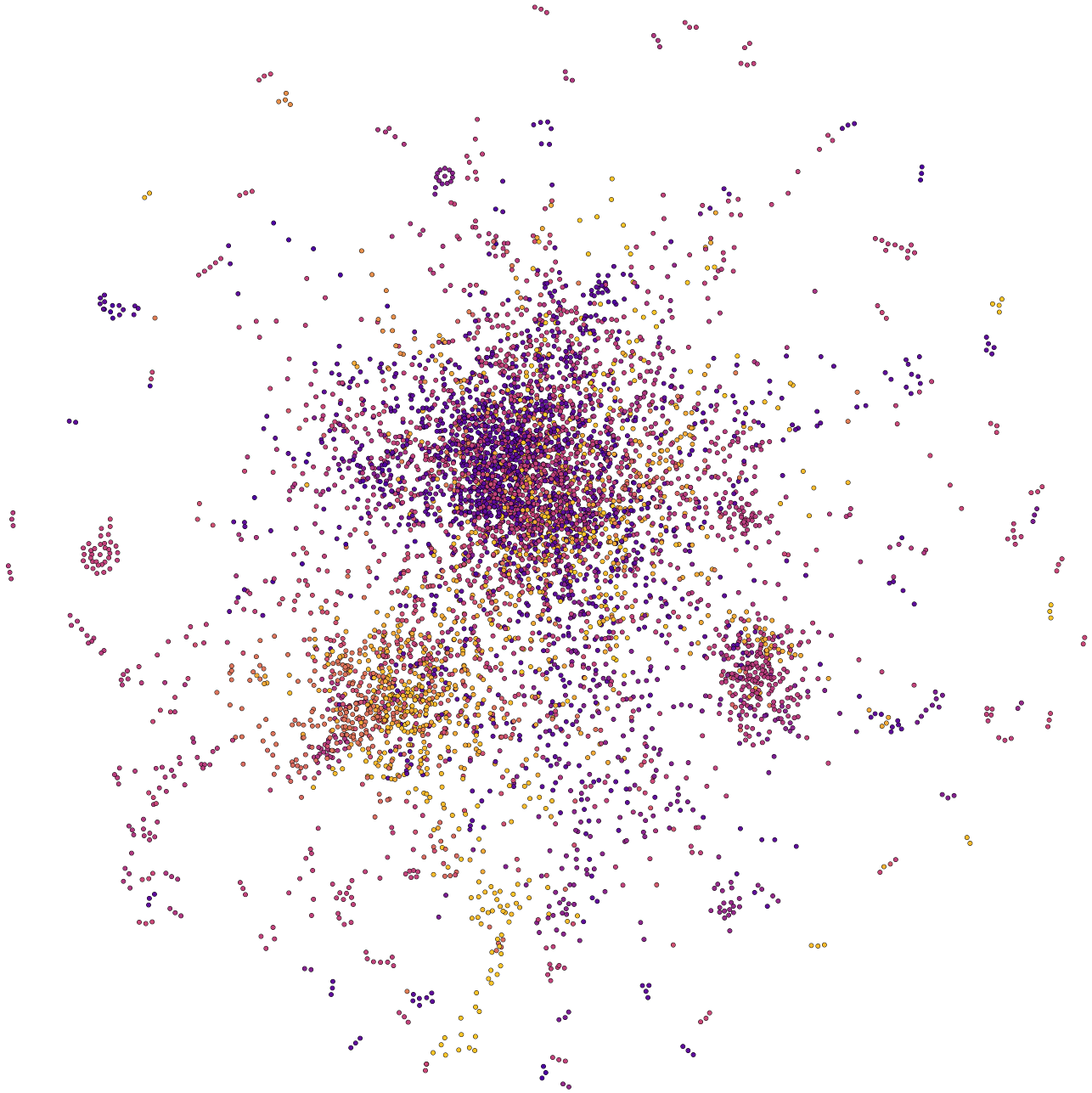
New reactions added to the network after manual curation:

- **Reactions from dashed lines = 820**
- **Reactions between different pathways = 26**

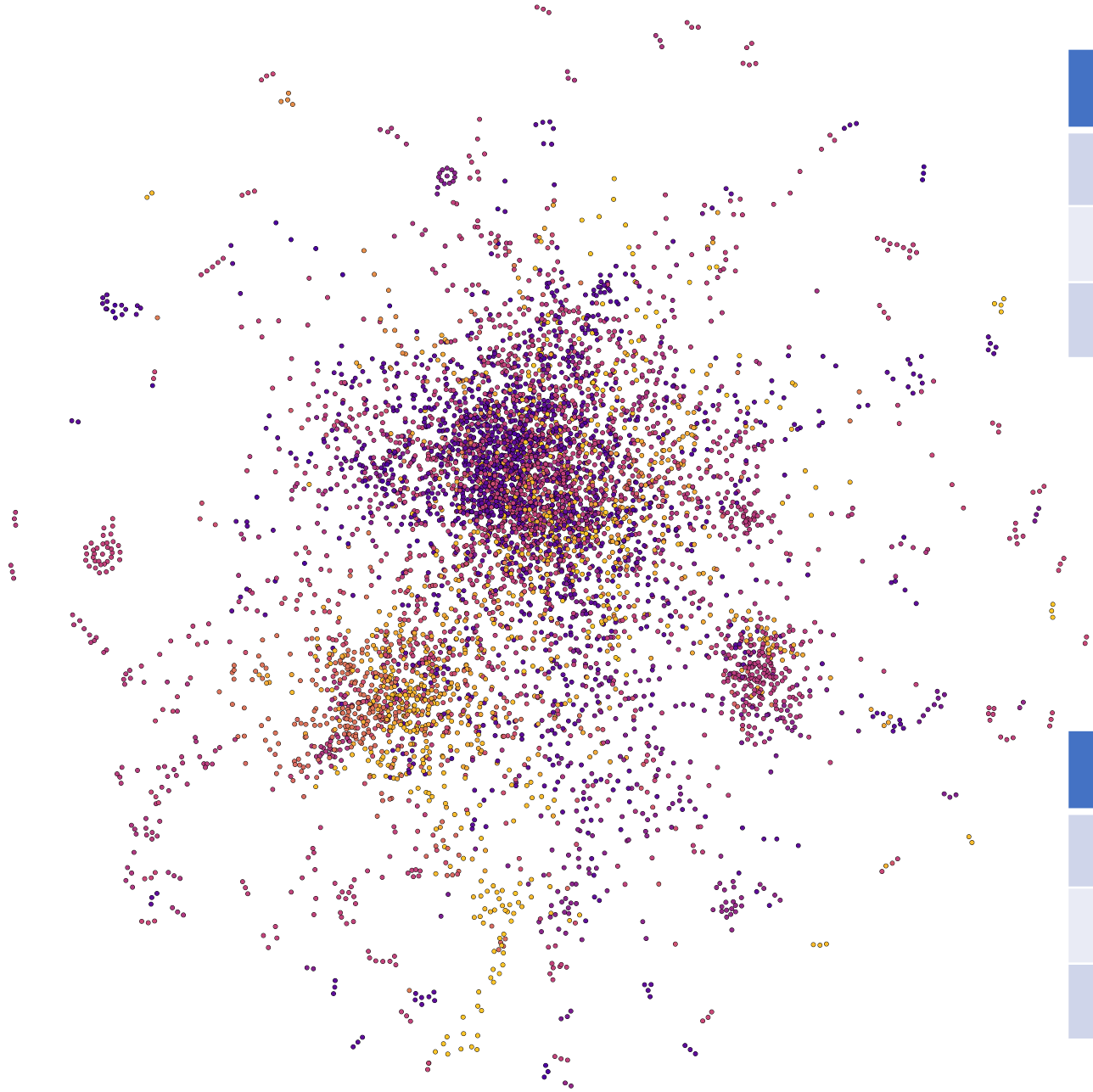
From Reactome …



… to selected pathways network



From Reactome to selected pathways network

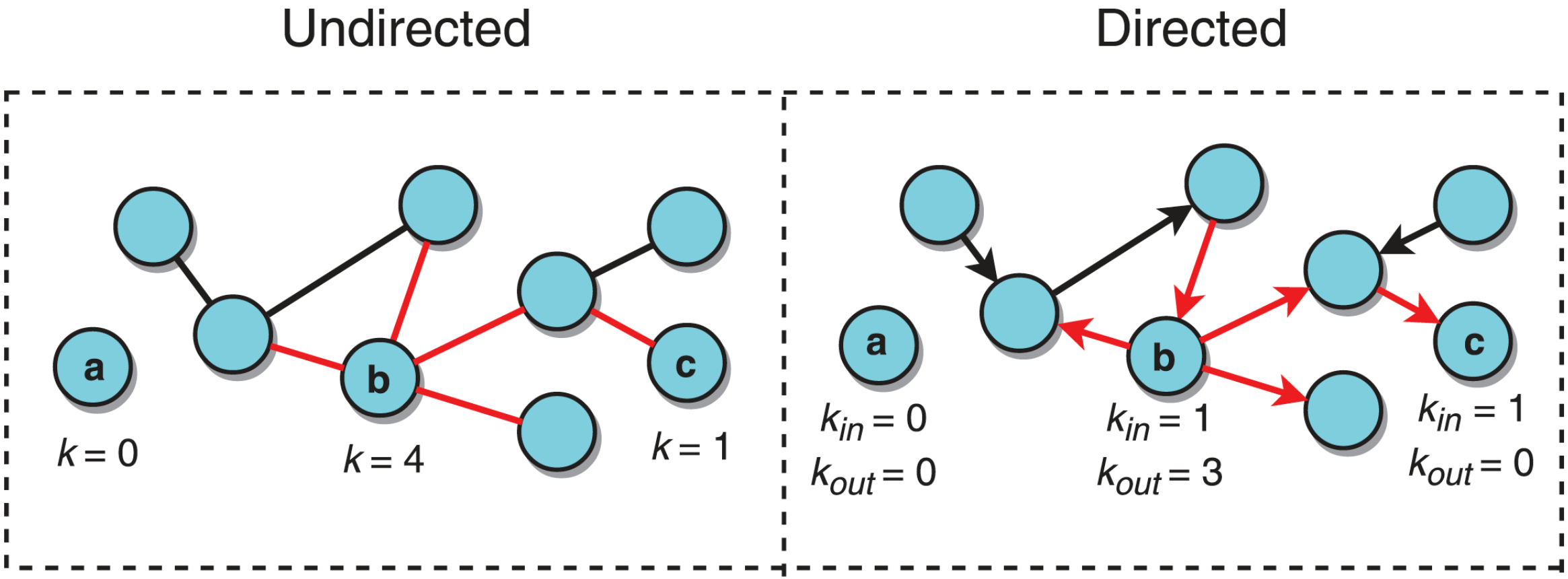


Reactome	
Pathways	2610
Species	23830
Connections	46834

Selected network	
Pathways	115
Species	5947
Connections	12040

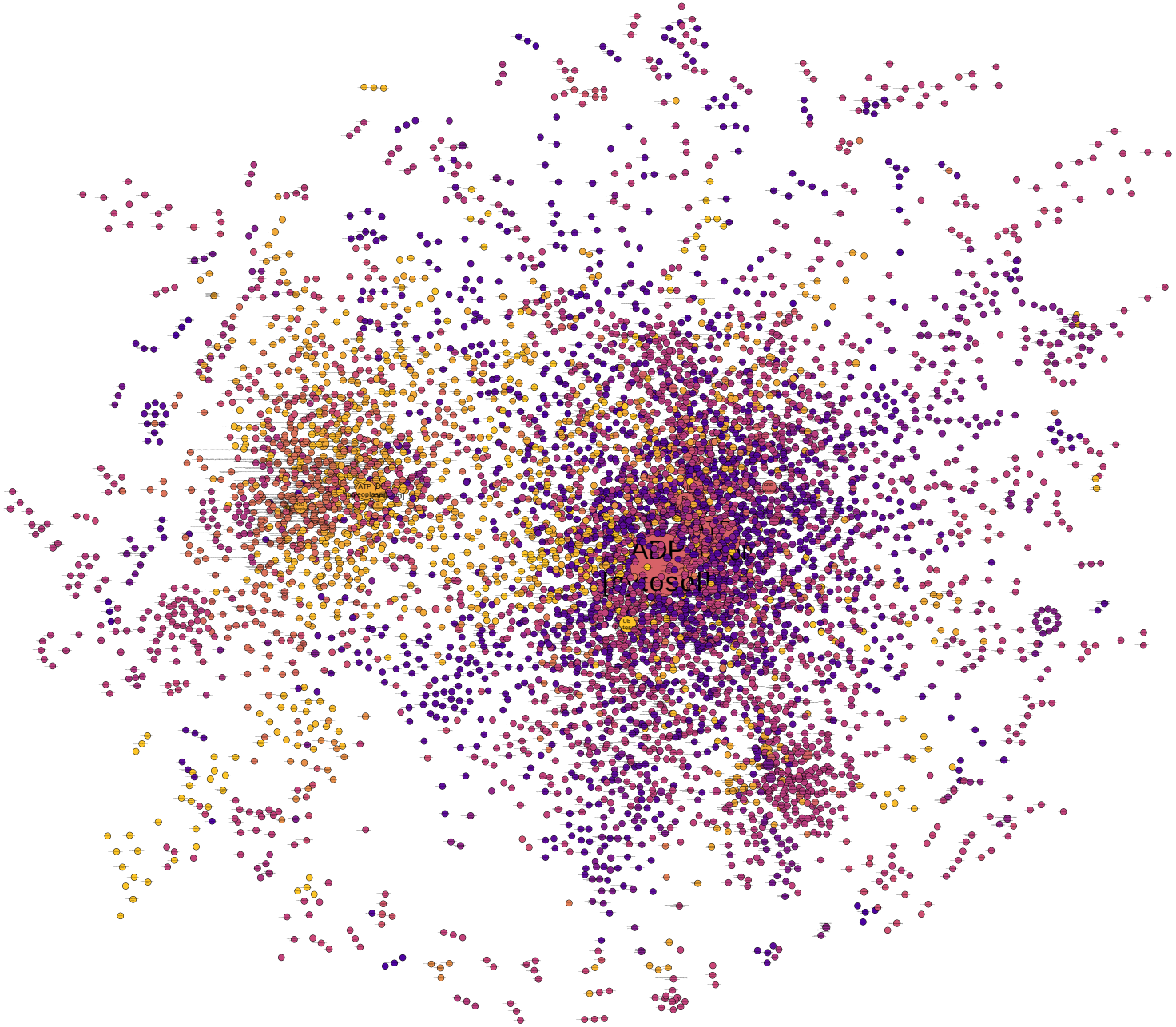
Analysis with concepts from network theory

Degree centrality



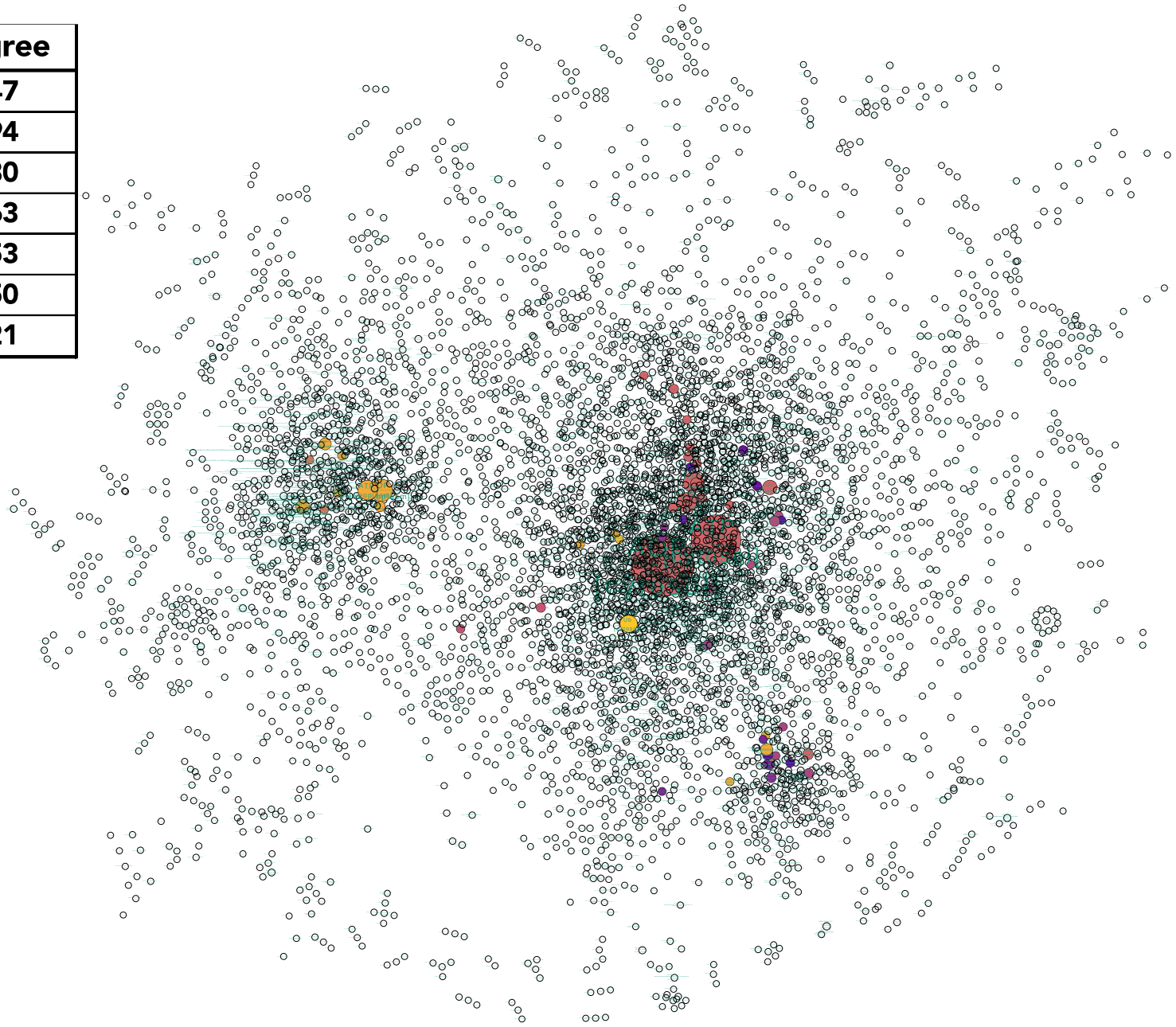
Menczer, Filippo, Santo Fortunato, and Clayton A. Davis. "A First Course in Network Science." Cambridge University Press, 2020

Degree centrality of the selected pathways network



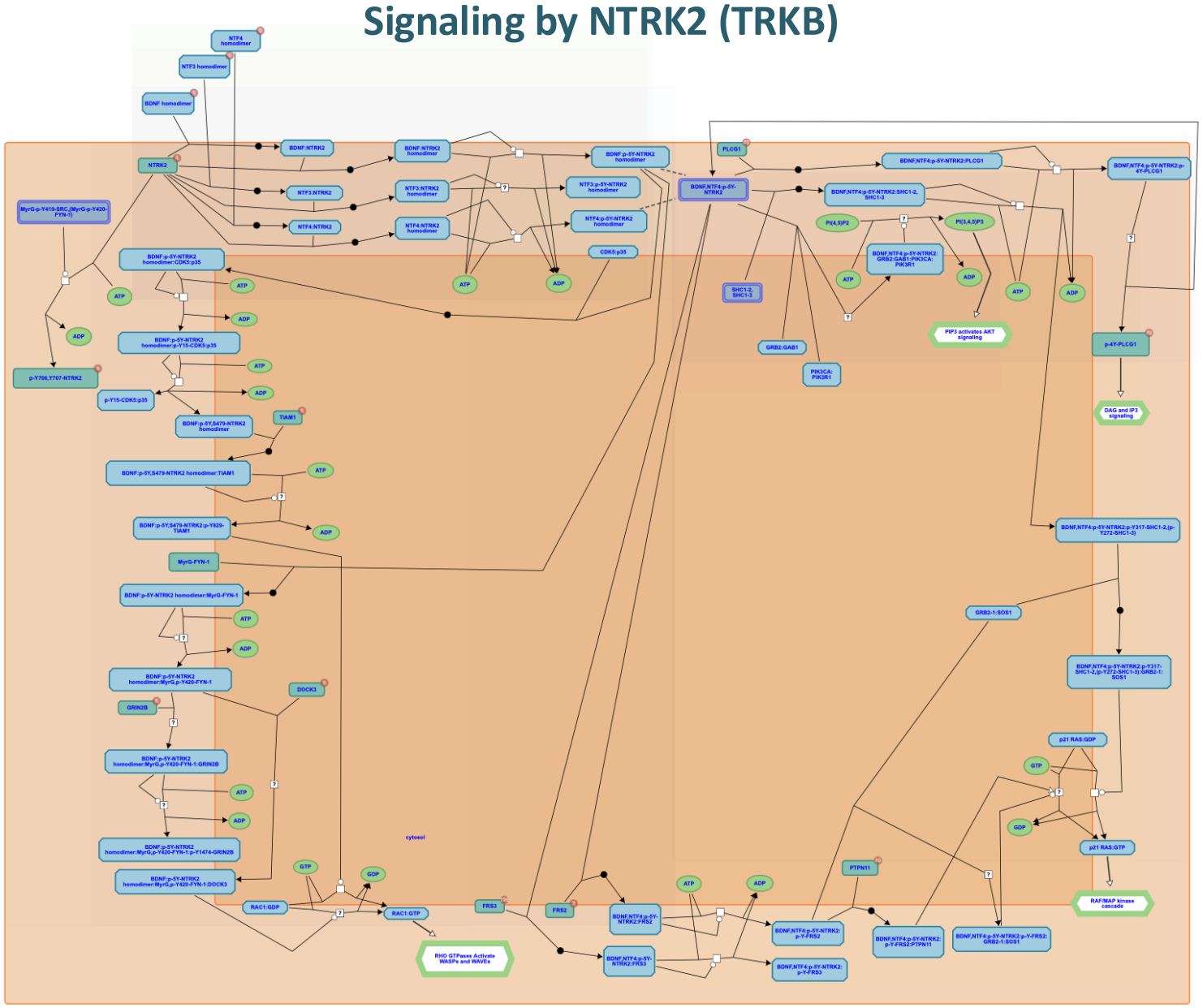
Degree centrality of the selected pathways network

Species	Degree
ADP [cytosol]	647
ATP [cytosol]	494
ADP [nucleoplasm]	180
H2O [cytosol]	163
Pi [cytosol]	153
ATP [nucleoplasm]	150
Ub [cytosol]	121



Co-factors identification and removal

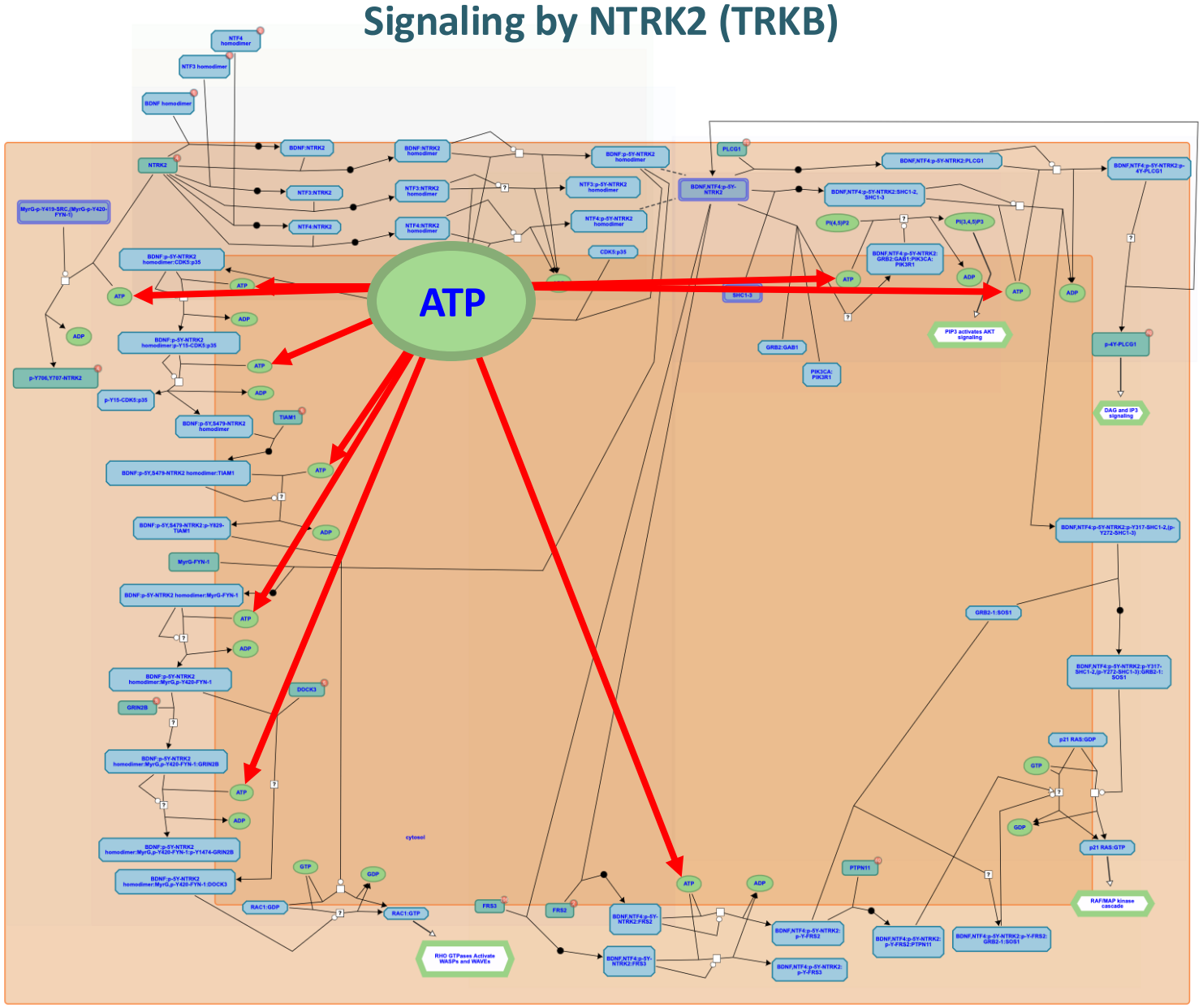
Why should we remove co-factors from the final network?



Co-factors identification and removal

Why should we remove co-factors from the final network?

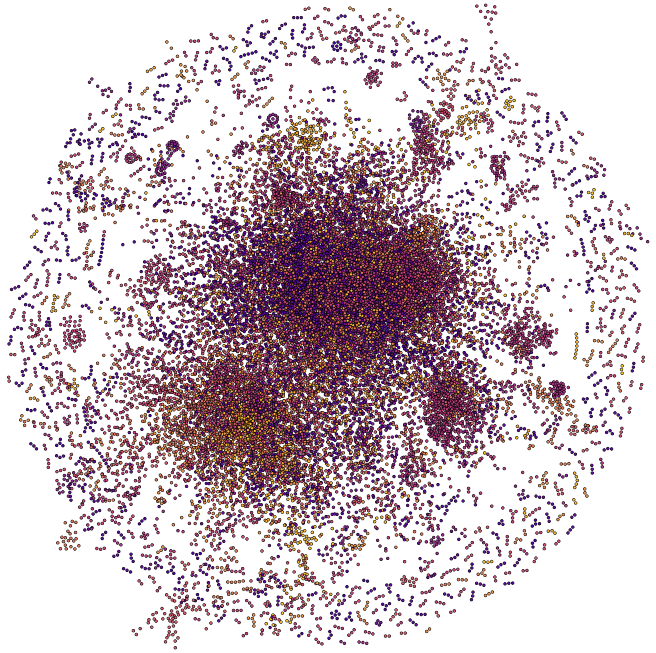
Avoid producing biological meaningless results.



Co-factors identification and removal

Selection of co-factor list for removal:

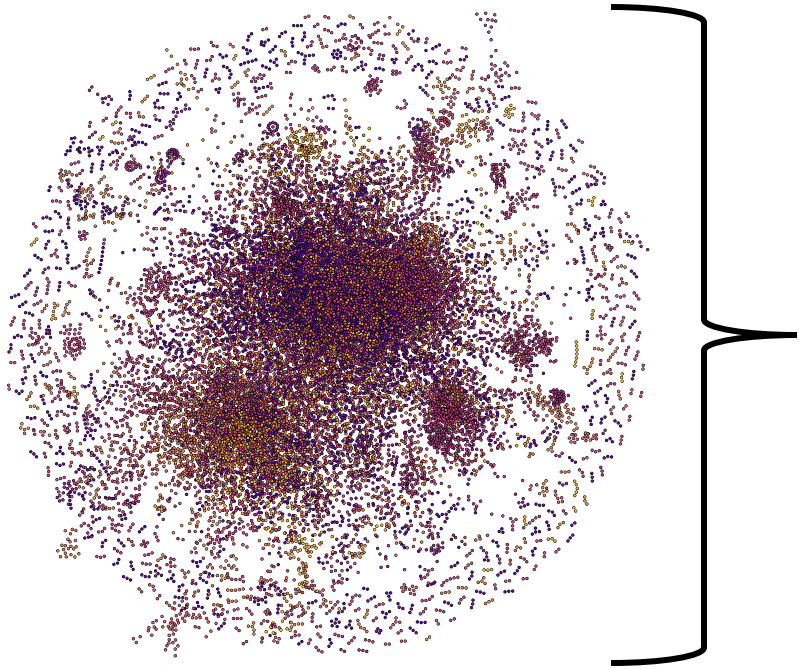
- Based on the degree ranking of the whole Reactome network.

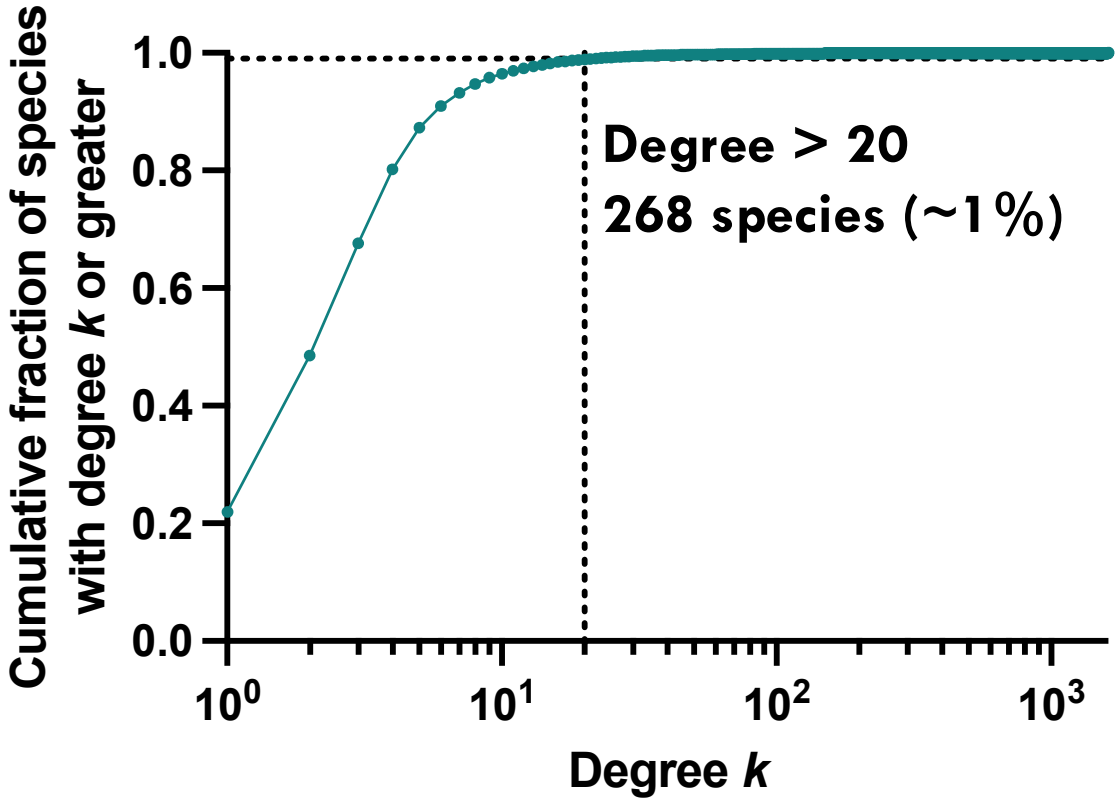


Co-factors identification and removal

Selection of co-factor list for removal:

- Based on the degree ranking of the whole Reactome network.

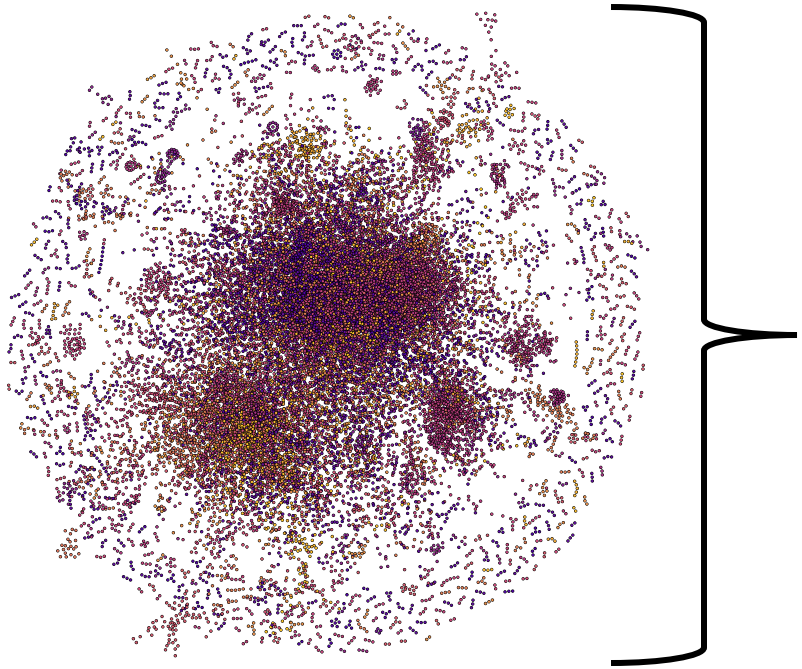


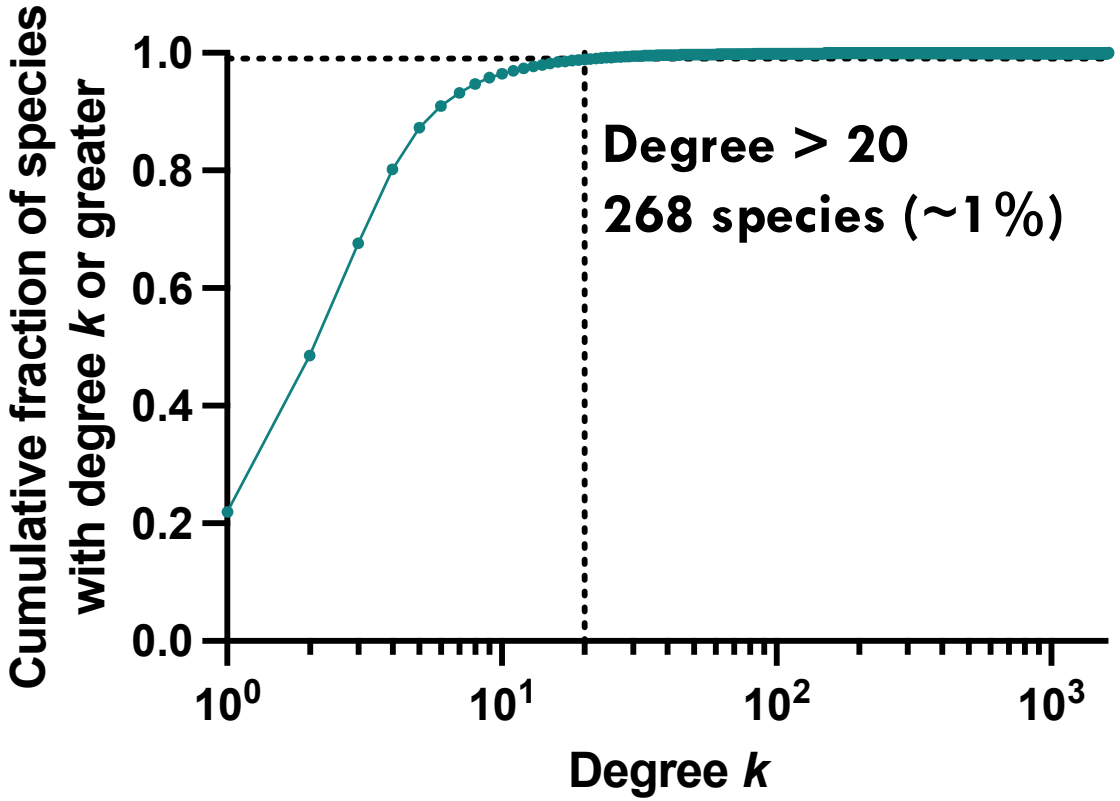


Co-factors identification and removal

Selection of co-factor list for removal:

- Based on the degree ranking of the whole Reactome network.





Keep important small second messengers:

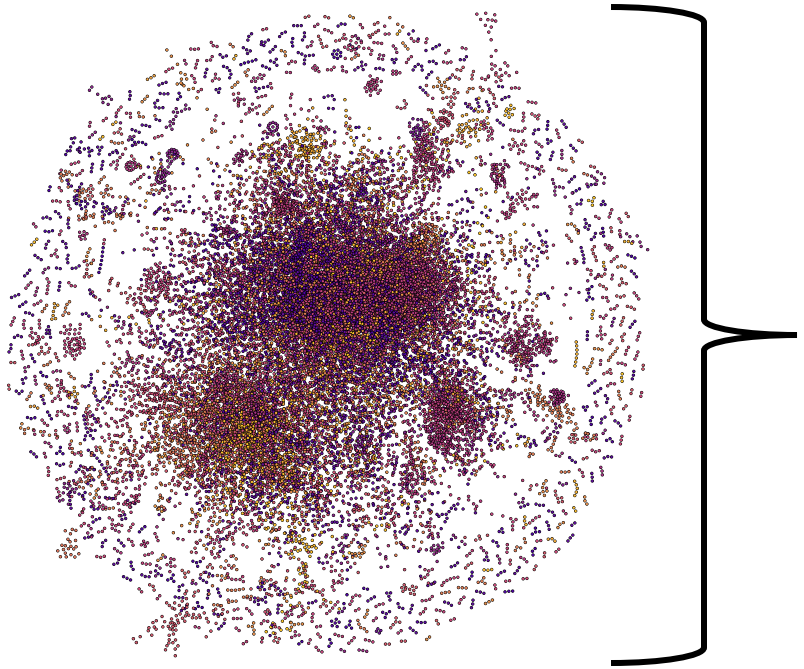
- cAMP
- cGMP
- IP_3
- DAG
- Ca^{2+}

Co-factors identification and removal

Selection of co-factor list for removal:

- Based on the degree ranking of the whole Reactome network.

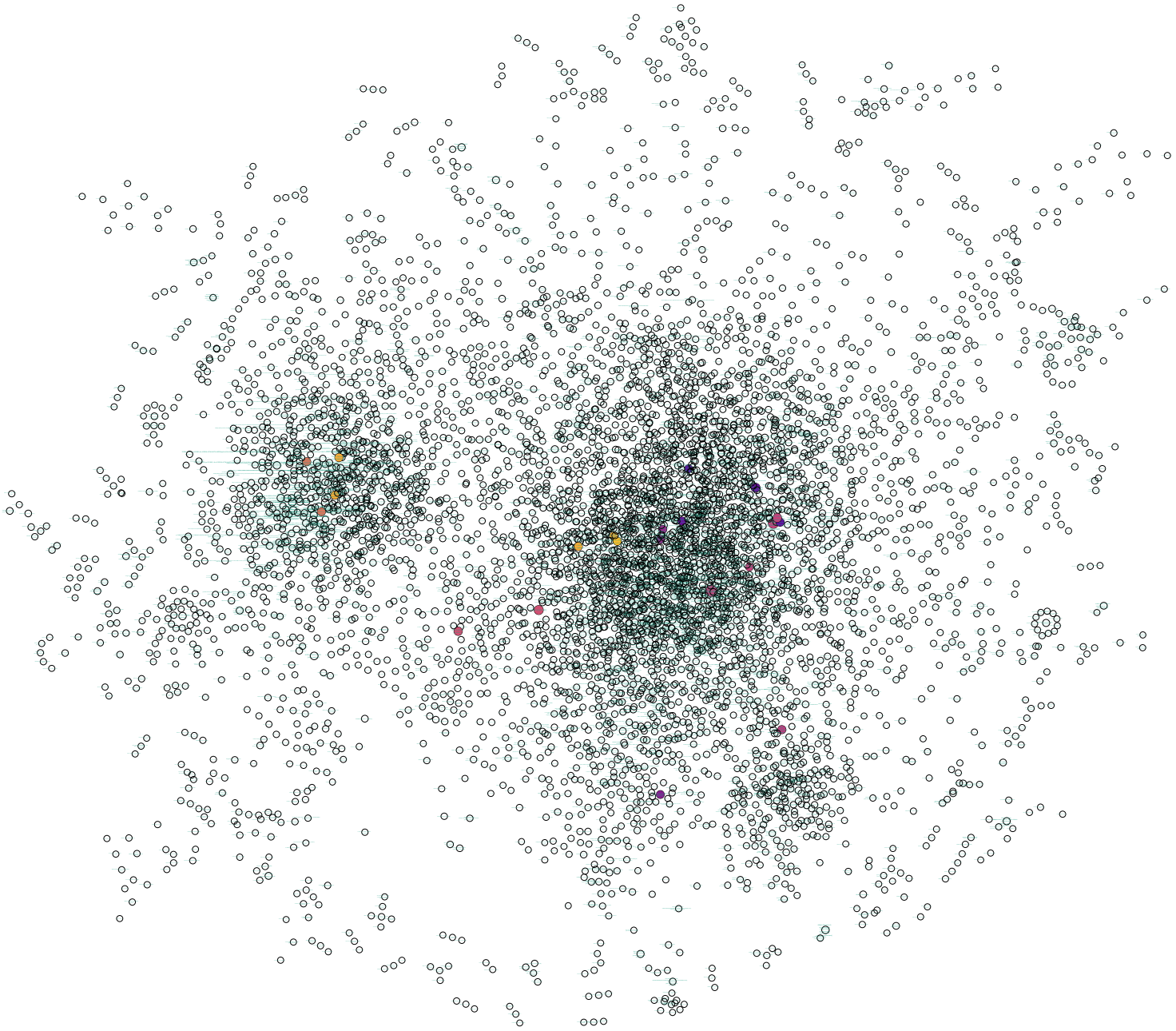
Keep important small second messengers:



54 co-factors, small molecules

ATP	Pi	Ac-CoA	Fe2+	IMP
ADP	PPi	GSH	Mg2+	NTP(4-)
AMP	H+	GSSG	Zn2+	NO
CTP	H2O	PAPS	NTP	HCOOH
CDP	Ub	PAP	K+	QH2
CMP	NAD+	AdoMet	Cl-	THF
GTP	NADH	AdoHcy	NH4+	
GDP	NADP+	K63polyUb	CH2O	
GMP	NADPH	H2O2	NH3	
UTP	O2	Na+	dNTP	
UDP	CO2	FADH2	BH4	
UMP	CoA-SH	FAD	HCO3-	

Co-factors identification and removal

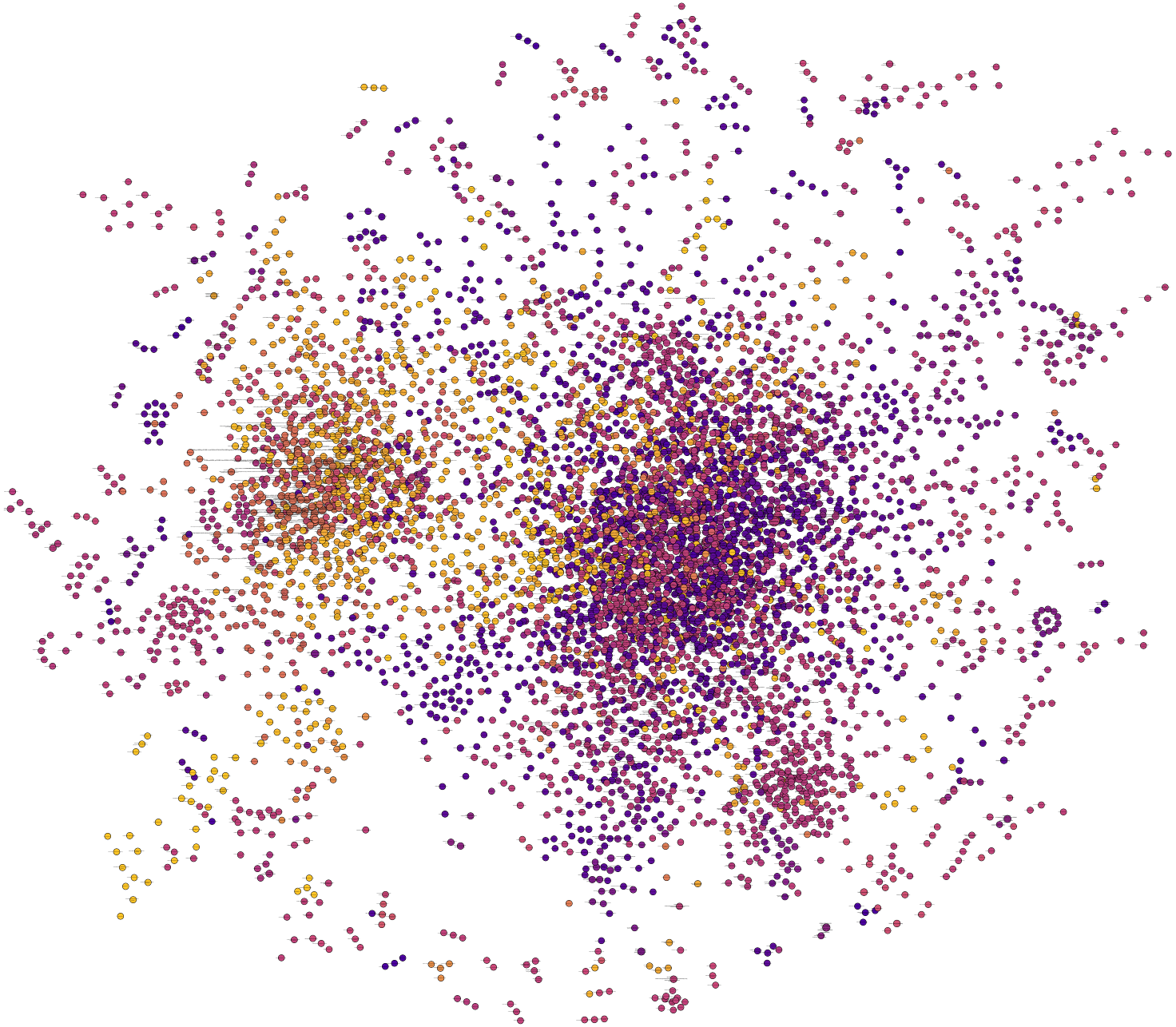


Selected network	
Pathways	115
Species	5947
Connections	12040

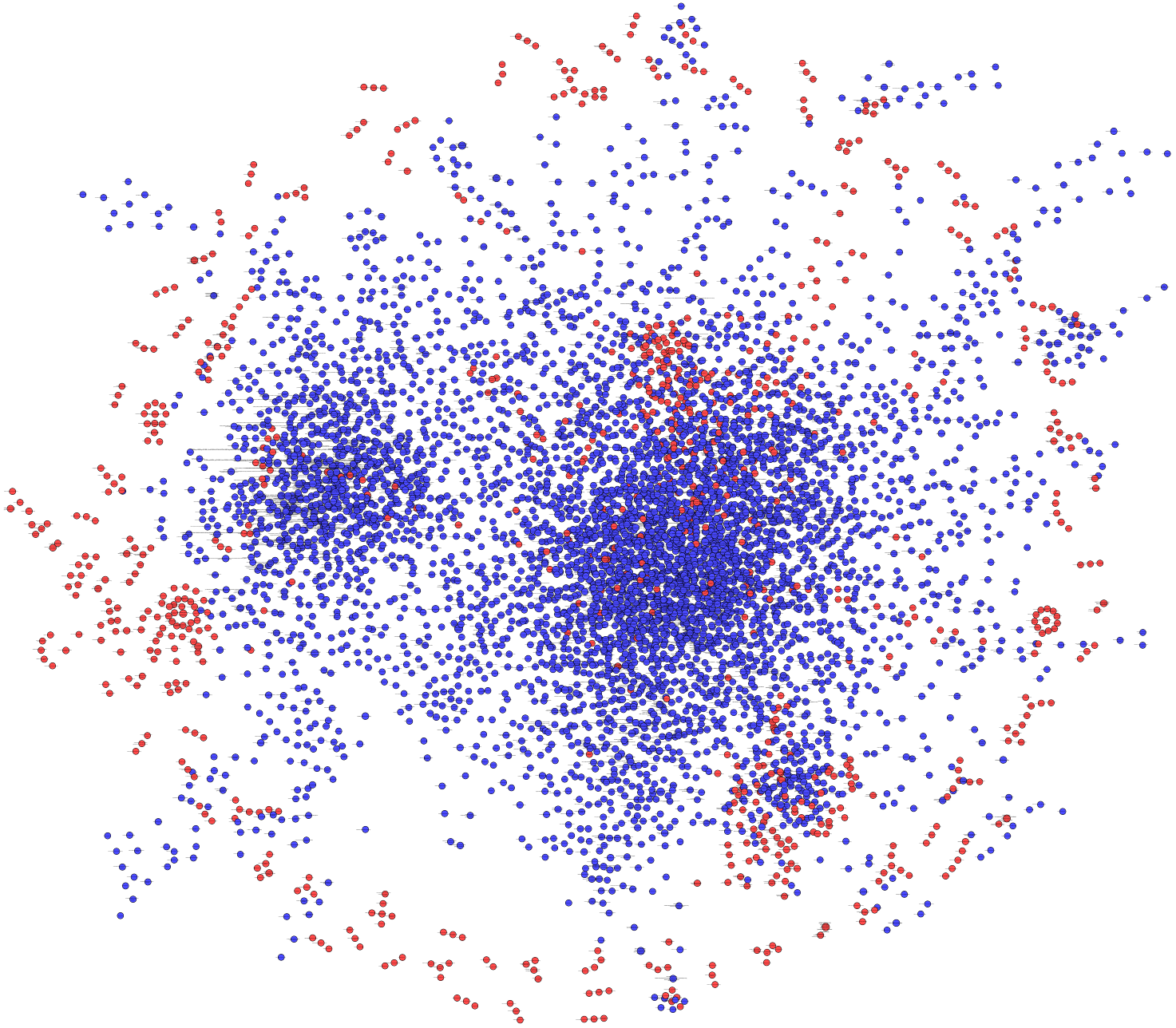
-136 species
-3344 connections

Final network	
Pathways	115
Species	5811
Connections	8696

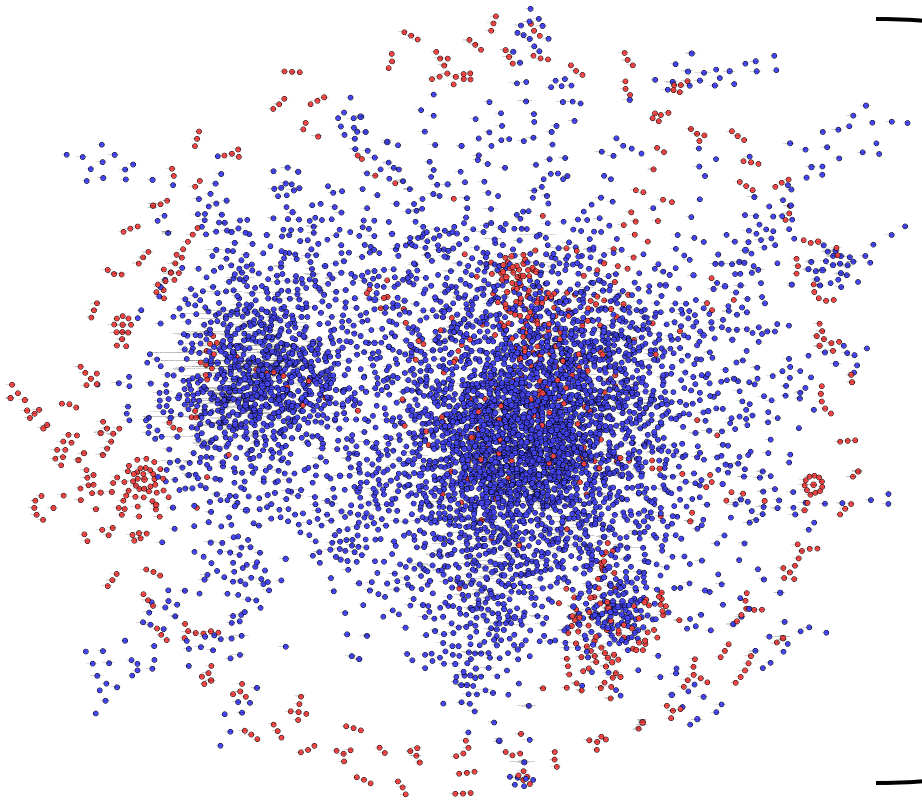
Final network of selected pathways

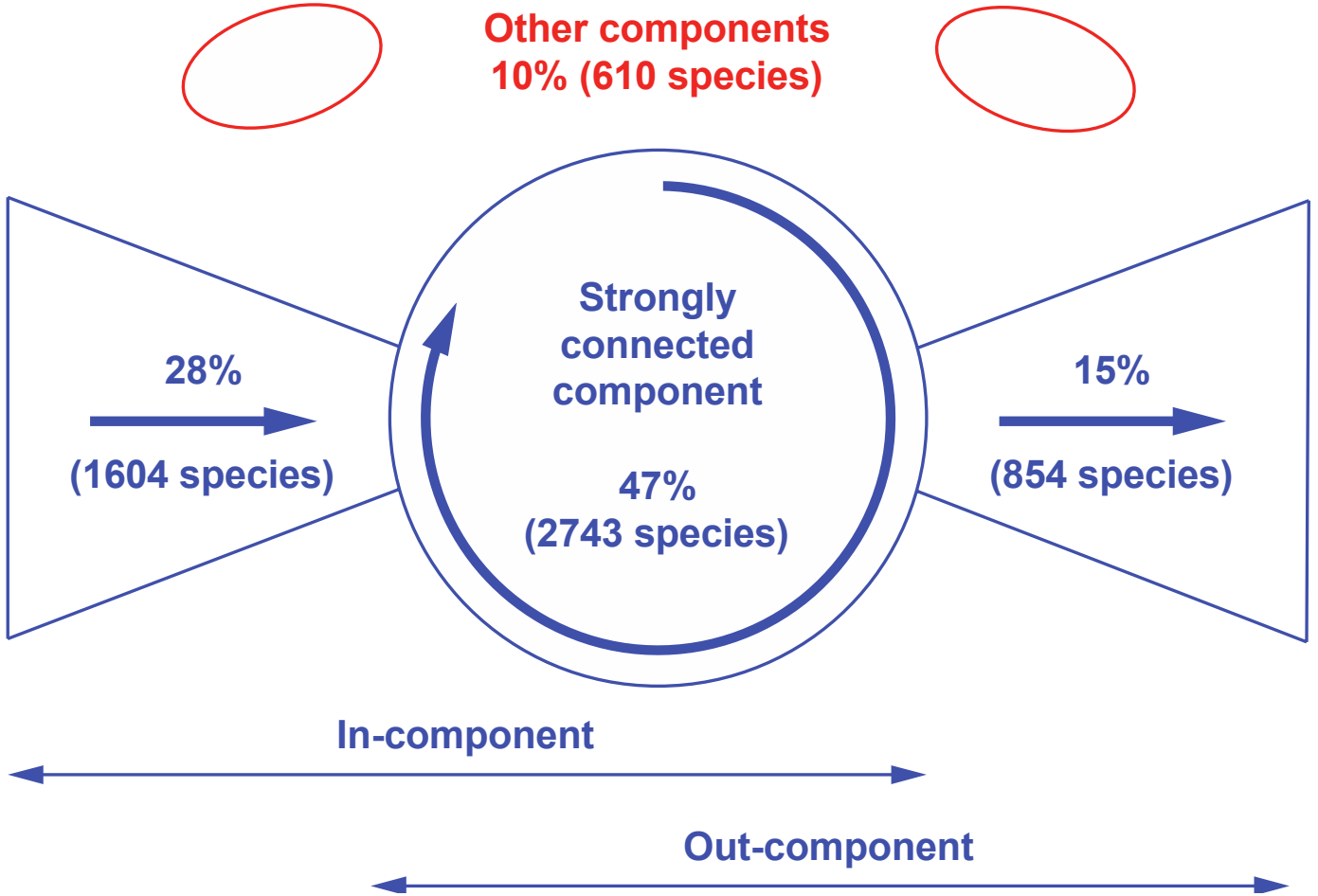


Analysis of the final network of selected pathways



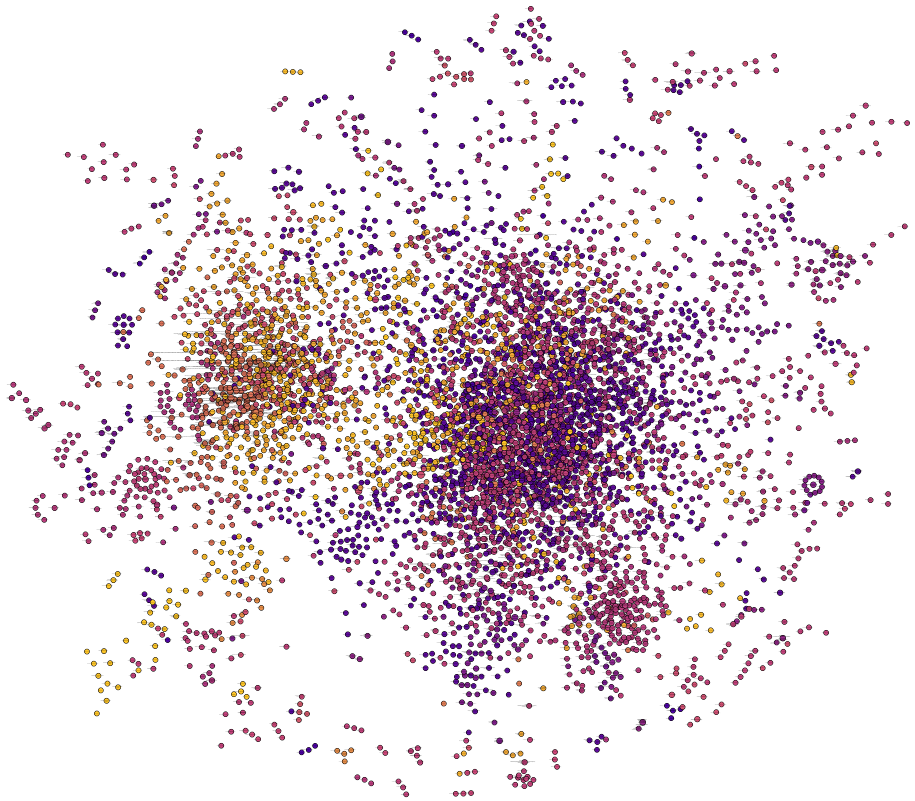
Analysis of the final network of selected pathways

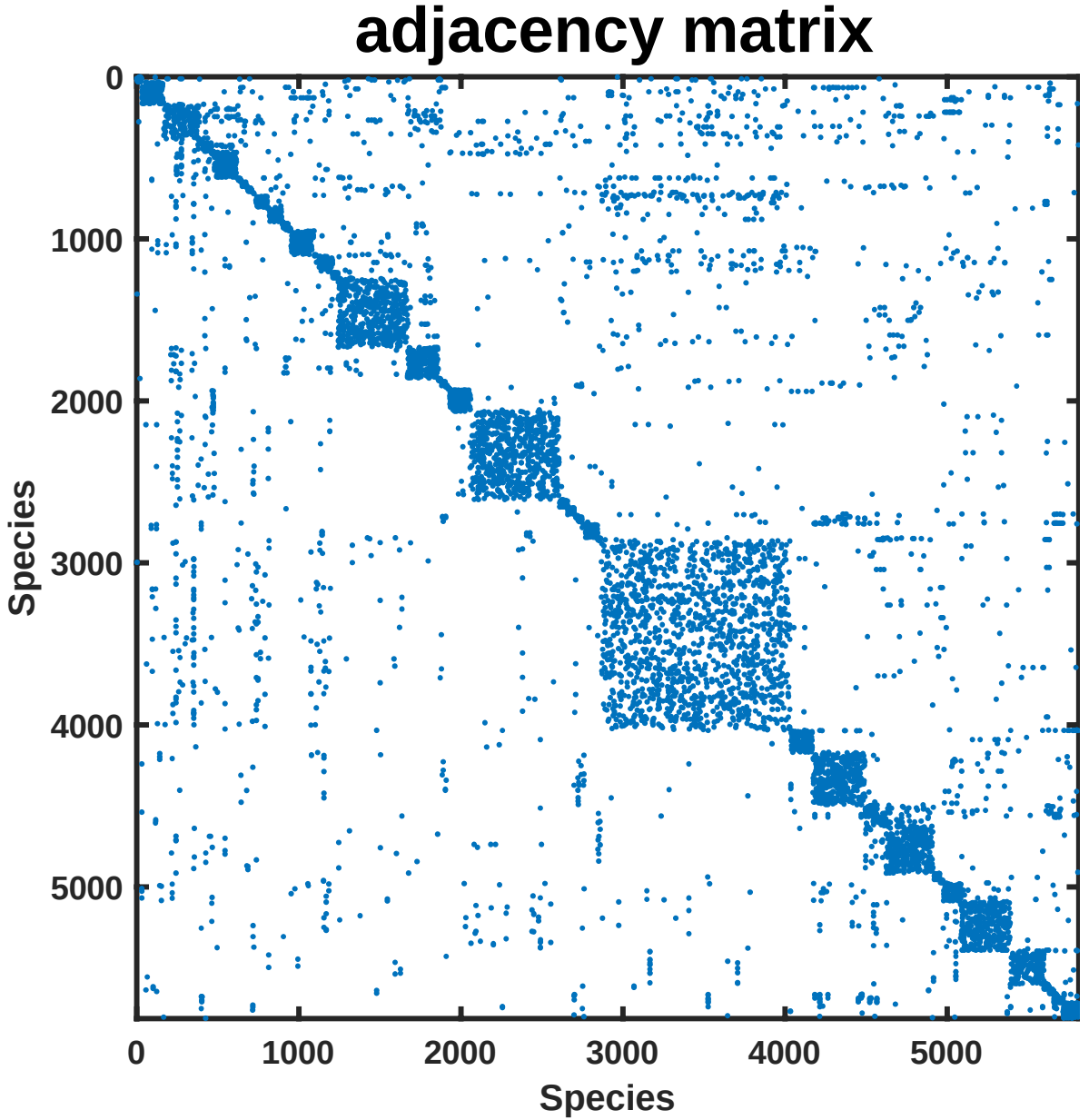




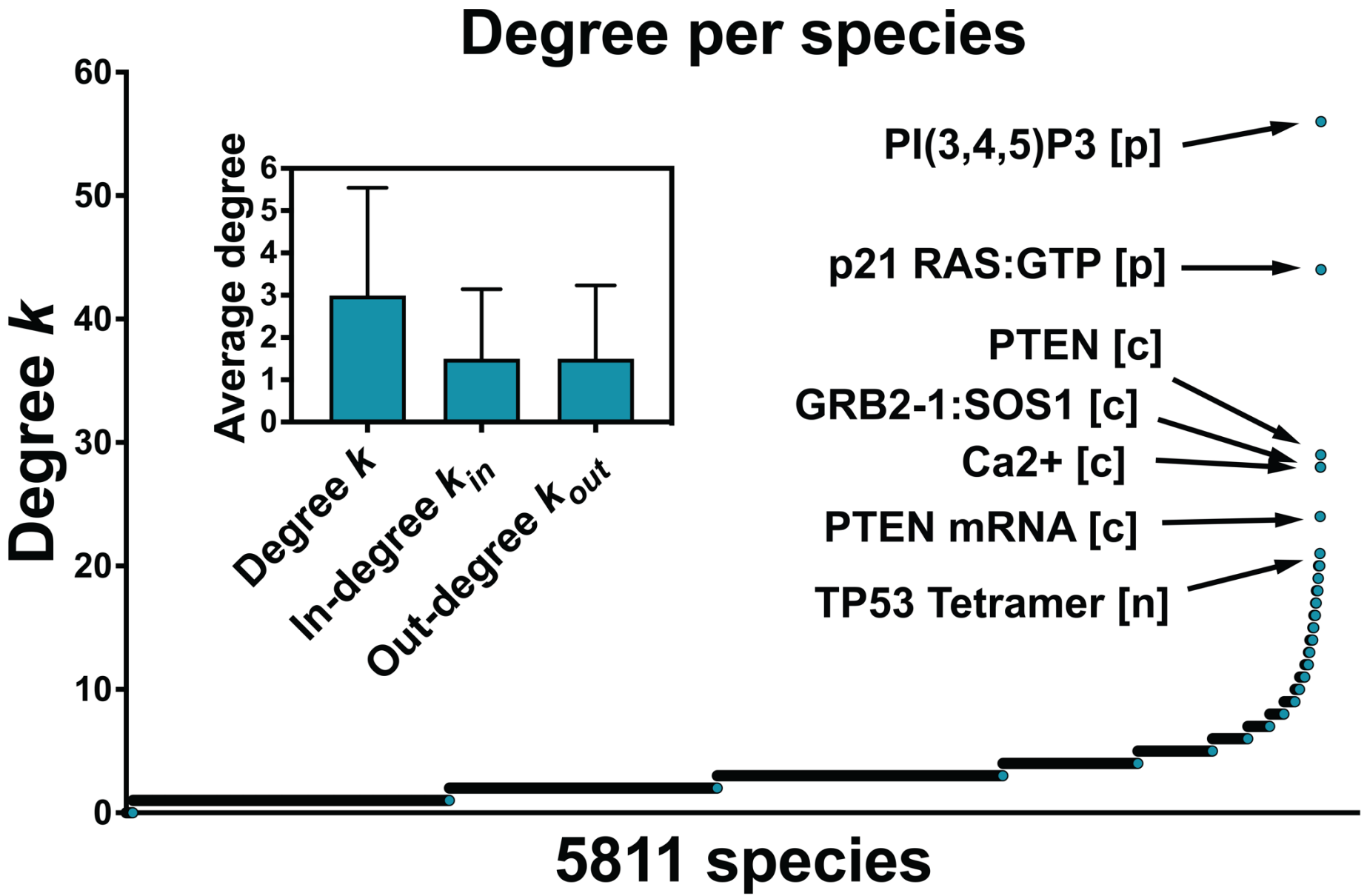
The "bow-tie" diagram

Analysis of the final network of selected pathways

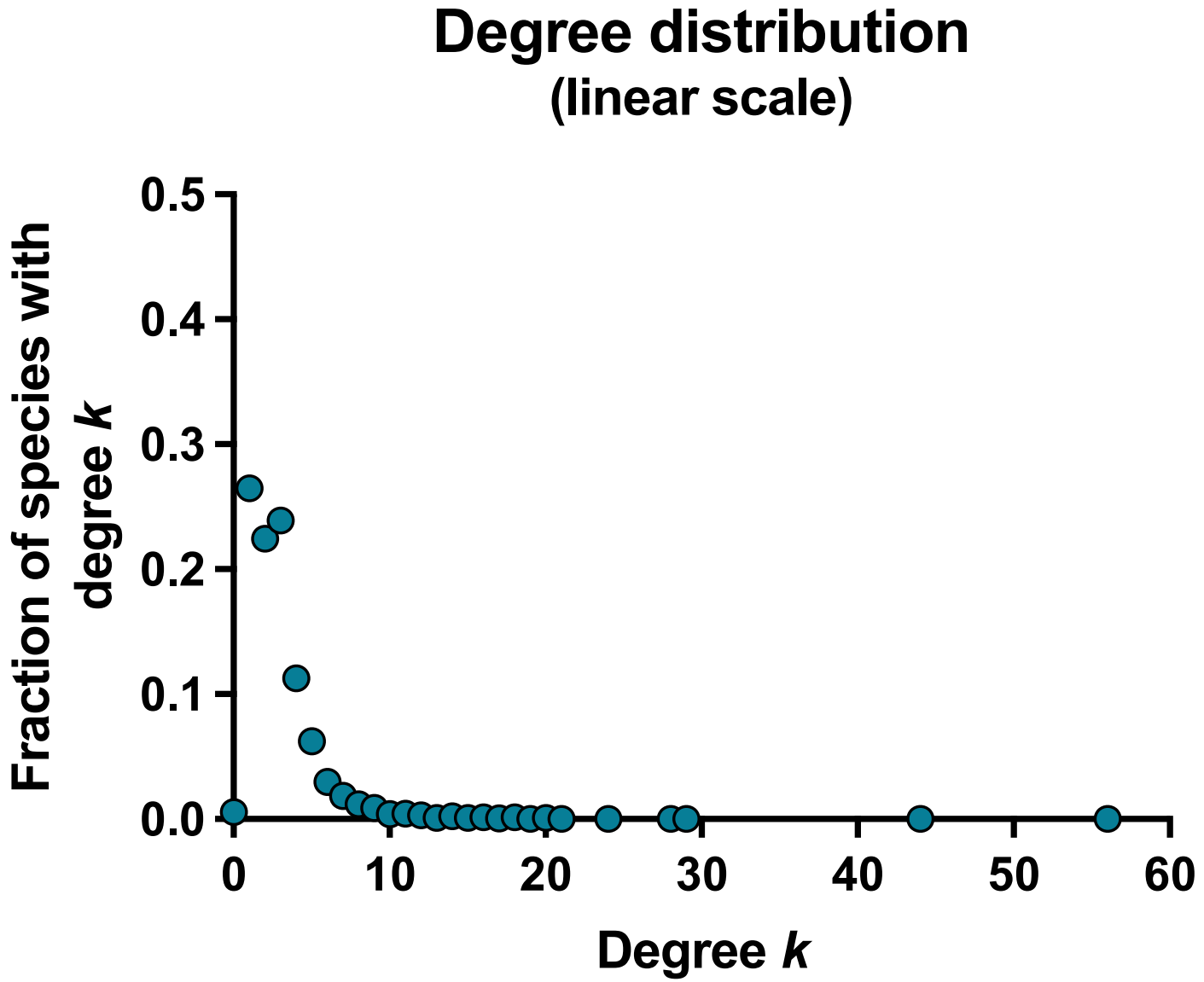




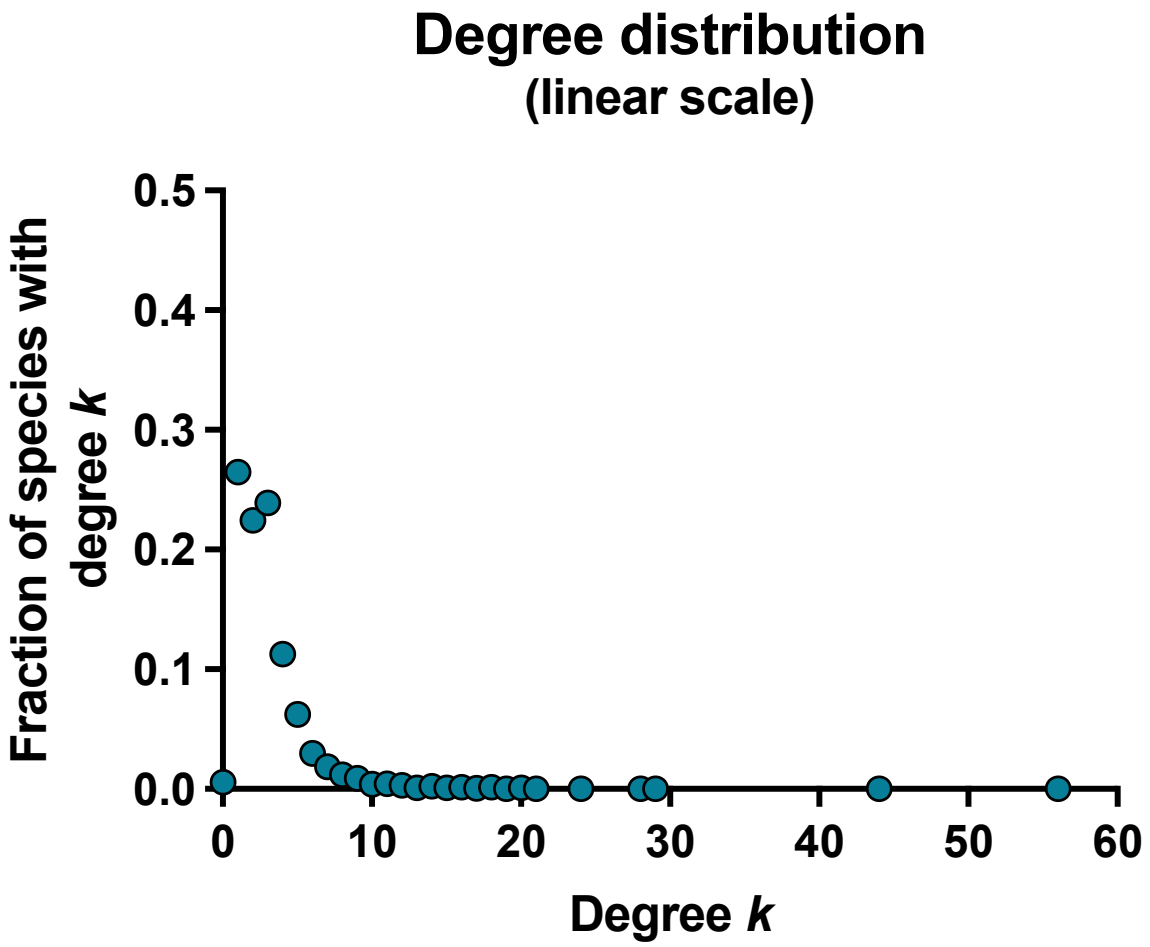
Analysis of the final network of selected pathways

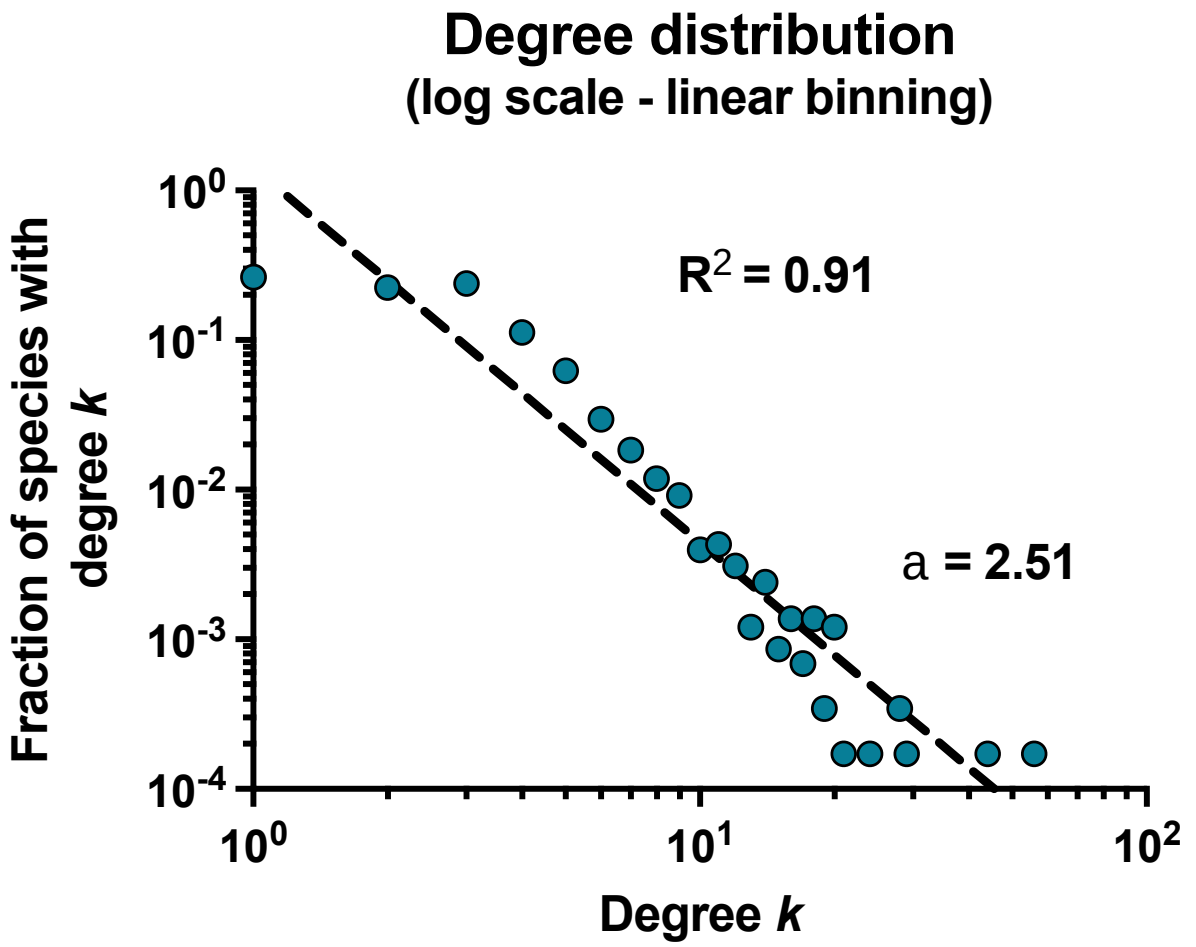


Analysis of the final network of selected pathways



Analysis of the final network of selected pathways



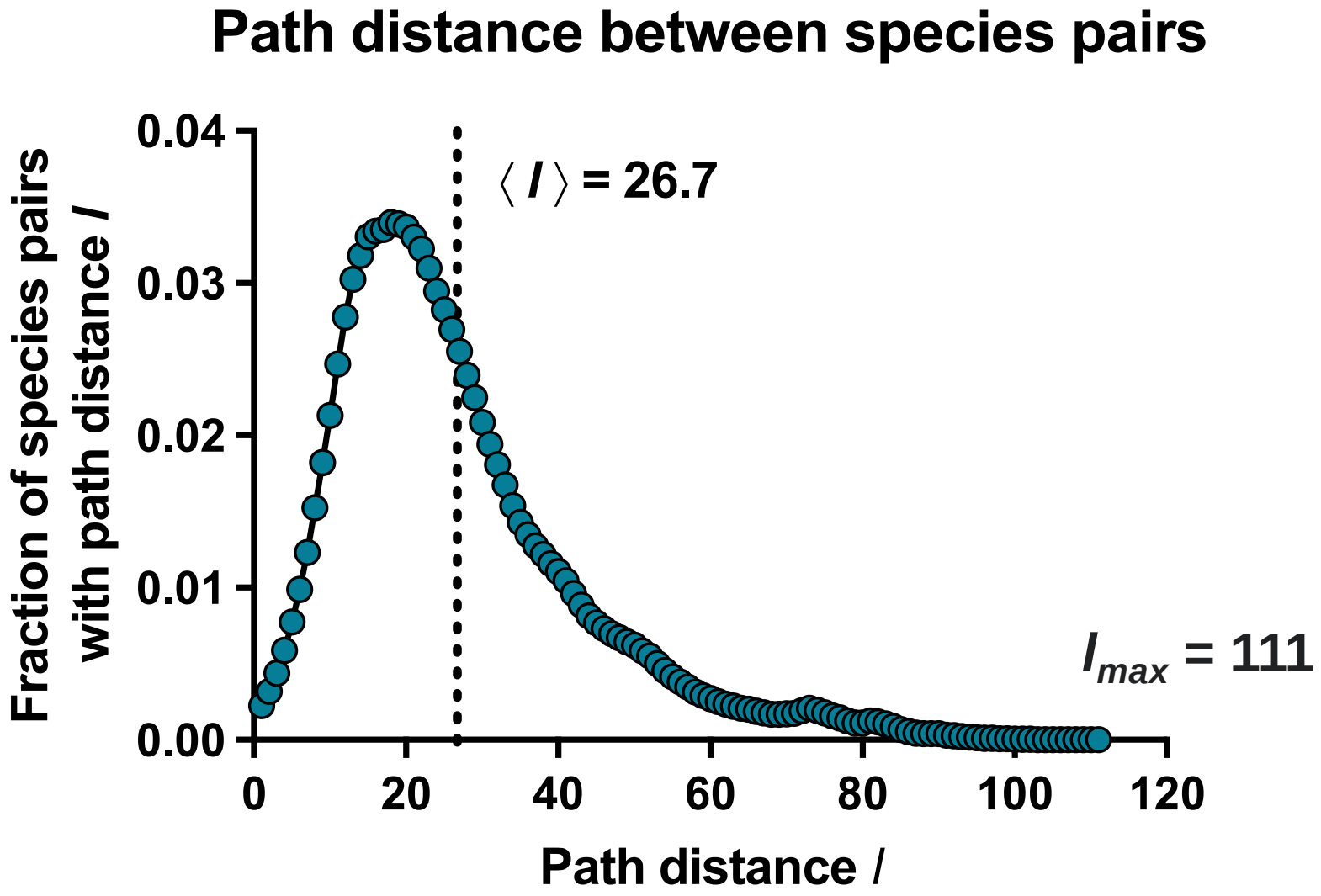


<u>*SCALE FREE*</u>

$$p_k \sim k^{-\alpha}$$

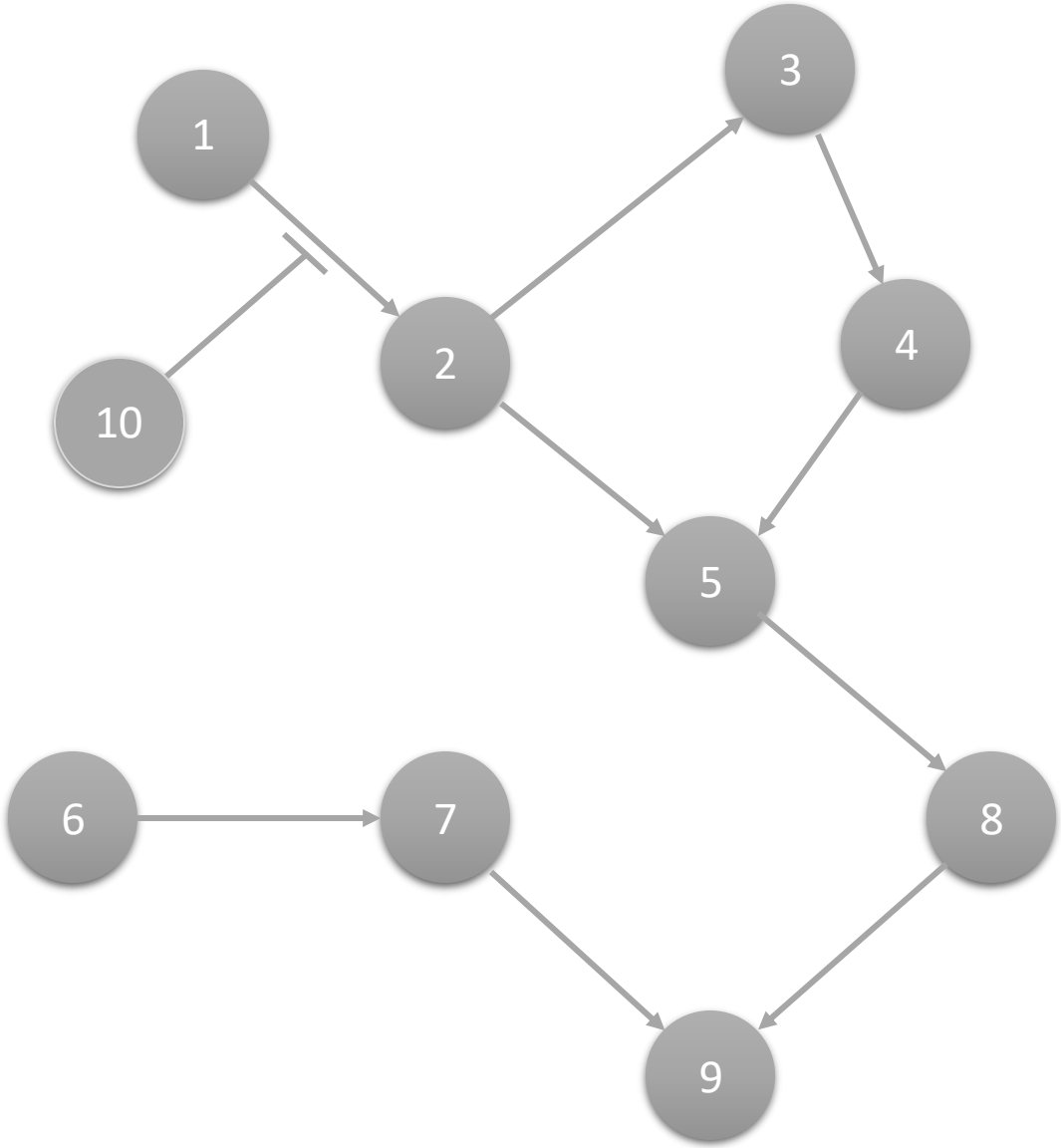
$$\log p_k \sim -\alpha \log k$$

Analysis of the final network of selected pathways



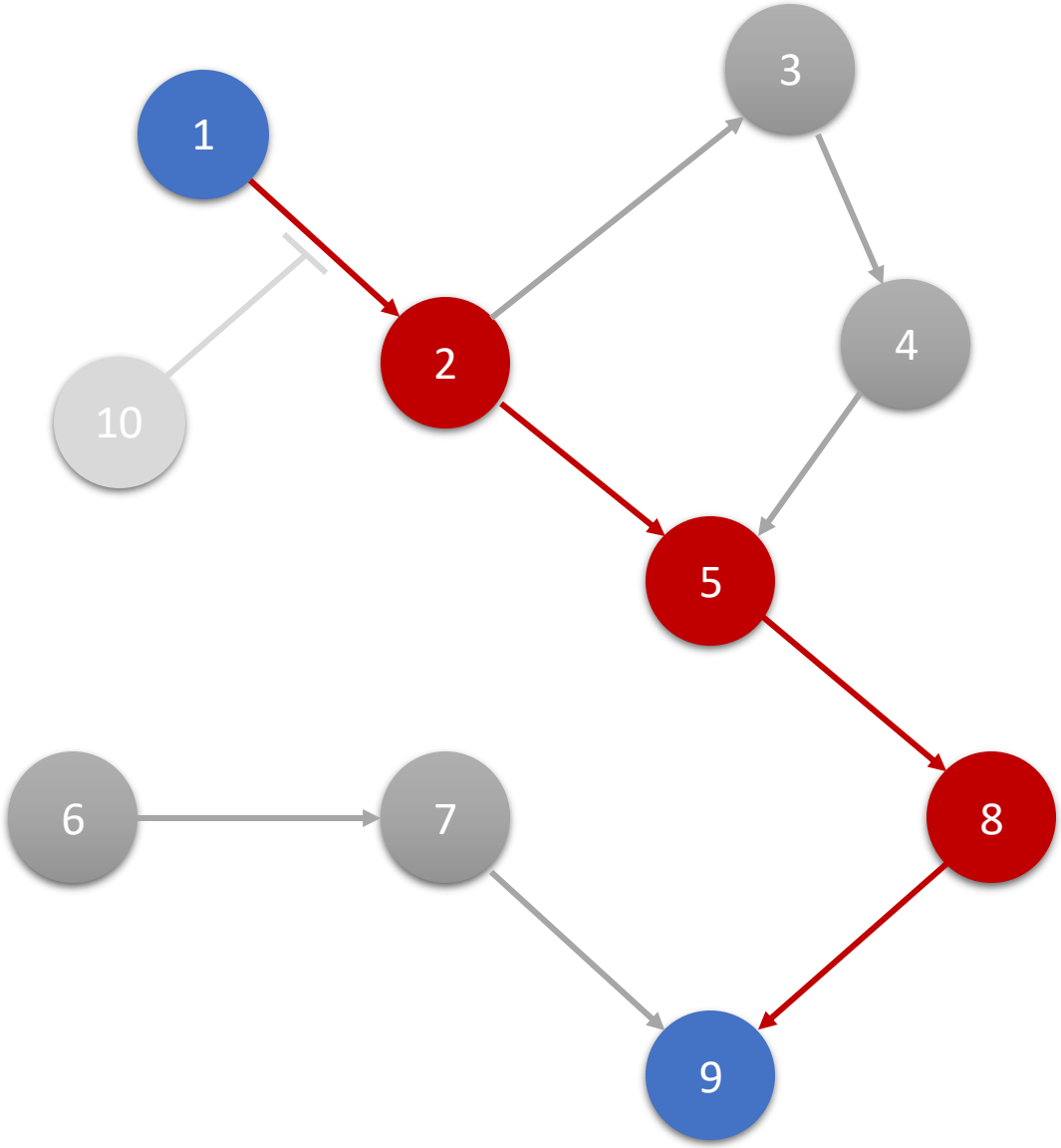
from Signaling Models to Information Flows

Method for connecting signaling network species



From species 1 to species 9

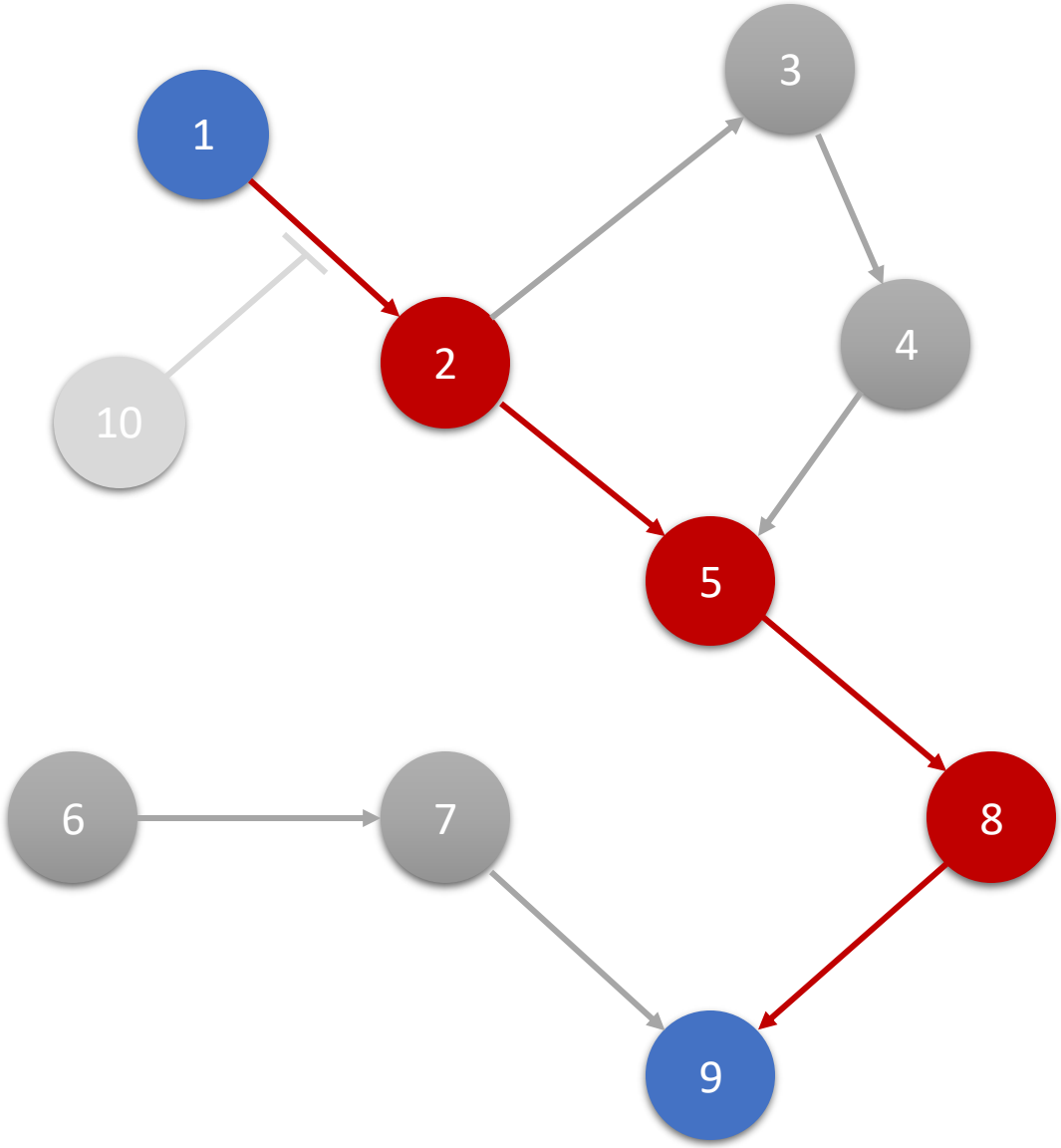
Method for connecting signaling network species



From species 1 to species 9

We enforce the start species (1) and the target species (9) to be active and minimize the number of active connections.

Method for connecting signaling network species

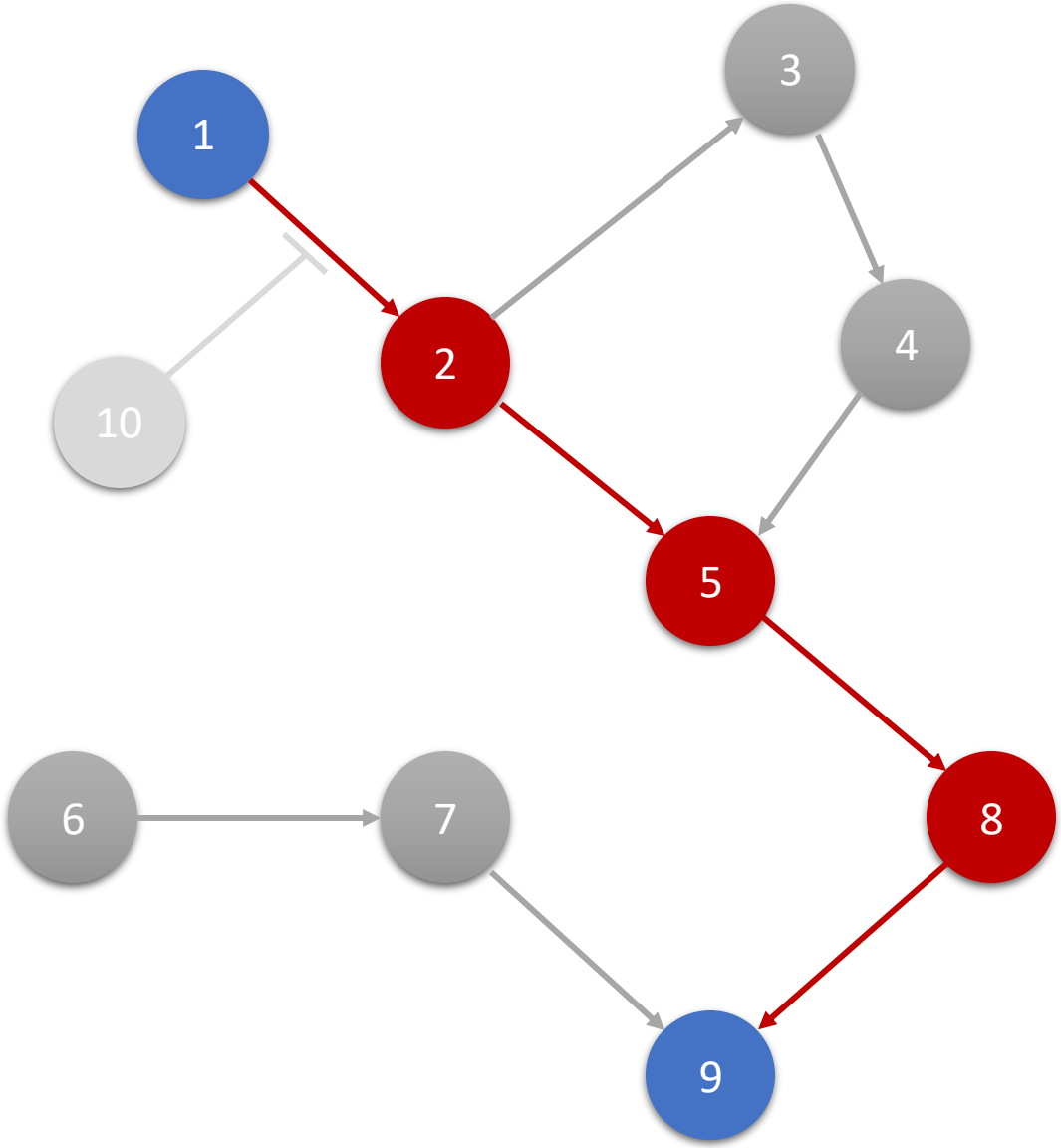


Why minimize?

1) Focus on the most essential species and connections of the information flow.

2) Identify the parsimonious way of cellular signal transduction.

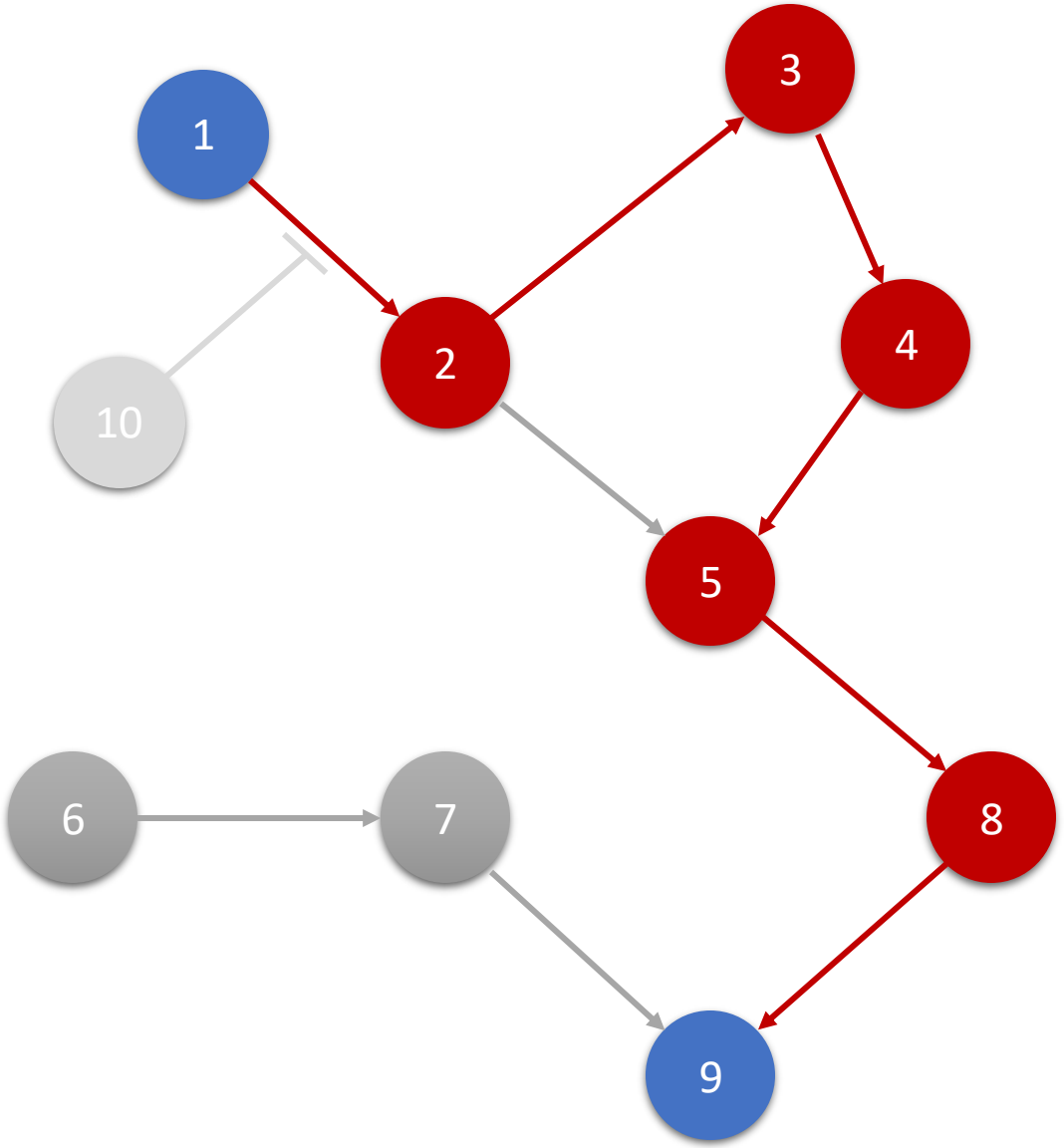
Method for connecting signaling network species



We exhaustively enumerate alternative paths!

Minimal path:
4 connections

Method for connecting signaling network species



We exhaustively enumerate alternative paths!

Minimal path:
4 connections

Alternative path:
Minimal path + 2

Studying BDNF connection to mTOR

The start species is the BDNF ligand.

What about the target species?
Need for a systematic way to identify target species.

Studying BDNF connection to mTOR

Start	Target
BDNF homodimer [e]	Active mTORC1 complex [l]
BDNF homodimer [e]	mTORC1 [c]
BDNF homodimer [e]	mTORC1 dimer [n]
BDNF homodimer [e]	mTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:GNP:RHEB:GTP [l]
BDNF homodimer [e]	MTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:RHEB:GTP [l]
BDNF homodimer [e]	MTORC1 with p-S722,S792-RPTOR:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]
BDNF homodimer [e]	mTORC1:p-T246-AKT1S1:YWHAB [l]
BDNF homodimer [e]	mTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]
BDNF homodimer [e]	MTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]
BDNF homodimer [e]	MTORC1:Ragulator:Rag:GNP:RHEB:GTP [l]
BDNF homodimer [e]	mTORC1:Ragulator:RagA,B:GTP:RagC,D:GDP:SLC38A9 [l]
BDNF homodimer [e]	mTORC1:RHEB:GTP:AKT1S1 [l]
BDNF homodimer [e]	mTORC1:RHEB:GTP:p-S183,T246-AKT1S1:YWHAB [l]
BDNF homodimer [e]	MTORC1:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]
BDNF homodimer [e]	mTORC1:RHEB:GTP:p-T246-AKT1S1 [l]
BDNF homodimer [e]	MTORC1:RHEB:GTP:ULK1:ATG13:RB1CC1:ATG101 [l]
BDNF homodimer [e]	v-ATPase:Ragulator:RRAGA,B:GDP:RRAGC,D:GDP:mTORC1:RHEB:GTP [l]
BDNF homodimer [e]	v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:mTORC1 [l]
BDNF homodimer [e]	v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:mTORC1:RHEB:GTP [l]

Studying BDNF connection to mTOR

Start	Target	Result
BDNF homodimer [e]	Active mTORC1 complex [l]	NO
BDNF homodimer [e]	mTORC1 [c]	NO
BDNF homodimer [e]	mTORC1 dimer [n]	NO
BDNF homodimer [e]	mTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:GNP:RHEB:GTP [l]	YES
BDNF homodimer [e]	MTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:RHEB:GTP [l]	YES
BDNF homodimer [e]	MTORC1 with p-S722,S792-RPTOR:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]	YES
BDNF homodimer [e]	mTORC1:p-T246-AKT1S1:YWHAB [l]	YES
BDNF homodimer [e]	mTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]	YES
BDNF homodimer [e]	MTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]	YES
BDNF homodimer [e]	MTORC1:Ragulator:Rag:GNP:RHEB:GTP [l]	NO
BDNF homodimer [e]	mTORC1:Ragulator:RagA,B:GTP:RagC,D:GDP:SLC38A9 [l]	NO
BDNF homodimer [e]	mTORC1:RHEB:GTP:AKT1S1 [l]	NO
BDNF homodimer [e]	mTORC1:RHEB:GTP:p-S183,T246-AKT1S1:YWHAB [l]	YES
BDNF homodimer [e]	MTORC1:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]	YES
BDNF homodimer [e]	mTORC1:RHEB:GTP:p-T246-AKT1S1 [l]	YES
BDNF homodimer [e]	MTORC1:RHEB:GTP:ULK1:ATG13:RB1CC1:ATG101 [l]	YES
BDNF homodimer [e]	v-ATPase:Ragulator:RRAGA,B:GDP:RRAGC,D:GDP:mTORC1:RHEB:GTP [l]	NO
BDNF homodimer [e]	v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:mTORC1 [l]	NO
BDNF homodimer [e]	v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:mTORC1:RHEB:GTP [l]	NO

Studying BDNF connection to mTOR

Start	Target	Result	Min path
BDNF homodimer [e]	Active mTORC1 complex [l]	NO	-
BDNF homodimer [e]	mTORC1 [c]	NO	-
BDNF homodimer [e]	mTORC1 dimer [n]	NO	-
BDNF homodimer [e]	mTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:GNP:RHEB:GTP [l]	YES	22
BDNF homodimer [e]	MTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:RHEB:GTP [l]	YES	23
BDNF homodimer [e]	MTORC1 with p-S722,S792-RPTOR:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]	YES	22
BDNF homodimer [e]	mTORC1:p-T246-AKT1S1:YWHAB [l]	YES	13
BDNF homodimer [e]	mTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]	YES	23
BDNF homodimer [e]	MTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]	YES	24
BDNF homodimer [e]	MTORC1:Ragulator:Rag:GNP:RHEB:GTP [l]	NO	-
BDNF homodimer [e]	mTORC1:Ragulator:RagA,B:GTP:RagC,D:GDP:SLC38A9 [l]	NO	-
BDNF homodimer [e]	mTORC1:RHEB:GTP:AKT1S1 [l]	NO	-
BDNF homodimer [e]	mTORC1:RHEB:GTP:p-S183,T246-AKT1S1:YWHAB [l]	YES	14
BDNF homodimer [e]	MTORC1:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]	YES	26
BDNF homodimer [e]	mTORC1:RHEB:GTP:p-T246-AKT1S1 [l]	YES	12
BDNF homodimer [e]	MTORC1:RHEB:GTP:ULK1:ATG13:RB1CC1:ATG101 [l]	YES	25
BDNF homodimer [e]	v-ATPase:Ragulator:RRAGA,B:GDP:RRAGC,D:GDP:mTORC1:RHEB:GTP [l]	NO	-
BDNF homodimer [e]	v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:mTORC1 [l]	NO	-
BDNF homodimer [e]	v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:mTORC1:RHEB:GTP [l]	NO	-

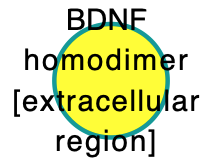
Studying BDNF connection to mTOR

Start	Target	Min path	No Alts Pmin	No Alts Pmin+1	No Alts Pmin+2	No Alts Pmin+3	Target Pathway
BDNF homodimer [e]	mTORC1:RHEB:GTP:p-T246-AKT1S1 [l]	12	1	1	-	-	MTOR
BDNF homodimer [e]	mTORC1:p-T246-AKT1S1:YWHAB [l]	13	1	1	-	-	MTOR
BDNF homodimer [e]	mTORC1:RHEB:GTP:p-S183,T246-AKT1S1:YWHAB [l]	14	1	1	-	-	MTOR
BDNF homodimer [e]	mTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:GNP:RHEB:GTP [l]	22	2	6	10	11	MTOR AMPK
BDNF homodimer [e]	mTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]	23	2	6	10	11	MTOR AMPK TP53
BDNF homodimer [e]	MTORC1 with p-S722,S792-RPTOR:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]	22	2	6	10	11	Macroautophagy
BDNF homodimer [e]	MTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:RHEB:GTP [l]	23	2	6	10	11	Macroautophagy
BDNF homodimer [e]	MTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]	24	2	6	10	11	Macroautophagy
BDNF homodimer [e]	MTORC1:RHEB:GTP:ULK1:ATG13:RB1CC1:ATG101 [l]	25	2	6	10	11	Macroautophagy
BDNF homodimer [e]	MTORC1:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]	26	2	6	10	11	Macroautophagy

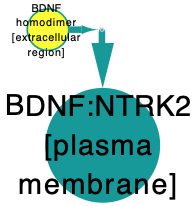
Studying BDNF connection to mTOR

Start	Target	Min path	No Alts Pmin	No Alts Pmin+1	No Alts Pmin+2	No Alts Pmin+3	Target Pathway
BDNF homodimer [e]	mTORC1:RHEB:GTP:p-T246-AKT1S1 [l]	12	1	1	-	-	MTOR
BDNF homodimer [e]	mTORC1:p-T246-AKT1S1:YWHAB [l]	13	1	1	-	-	MTOR
BDNF homodimer [e]	mTORC1:RHEB:GTP:p-S183,T246-AKT1S1:YWHAB [l]	14	1	1	-	-	MTOR
BDNF homodimer [e]	mTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:GNP:RHEB:GTP [l]	22	2	6	10	11	MTOR AMPK
BDNF homodimer [e]	mTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]	23	2	6	10	11	MTOR AMPK TP53
BDNF homodimer [e]	MTORC1 with p-S722,S792-RPTOR:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]	22	2	6	10	11	Macroautophagy
BDNF homodimer [e]	MTORC1 with p-S722,S792-RPTOR:Ragulator:Rag:RHEB:GTP [l]	23	2	6	10	11	Macroautophagy
BDNF homodimer [e]	MTORC1:Ragulator:Rag:GNP:RHEB:GDP [l]	24	2	6	10	11	Macroautophagy
BDNF homodimer [e]	MTORC1:RHEB:GTP:ULK1:ATG13:RB1CC1:ATG101 [l]	25	2	6	10	11	Macroautophagy
BDNF homodimer [e]	MTORC1:RHEB:GTP:p-S758-ULK1:ATG13:RB1CC1:ATG101 [l]	26	2	6	10	11	Macroautophagy

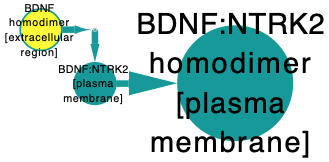
Studying BDNF connection to mTOR



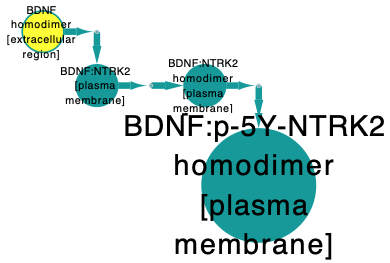
Studying BDNF connection to mTOR



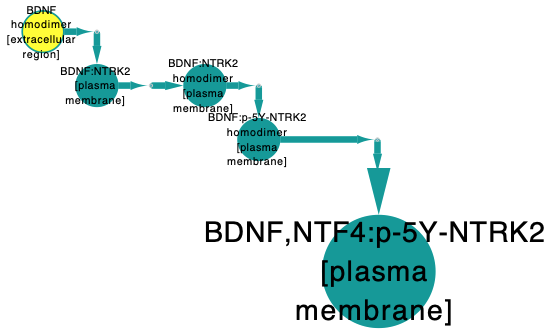
Studying BDNF connection to mTOR



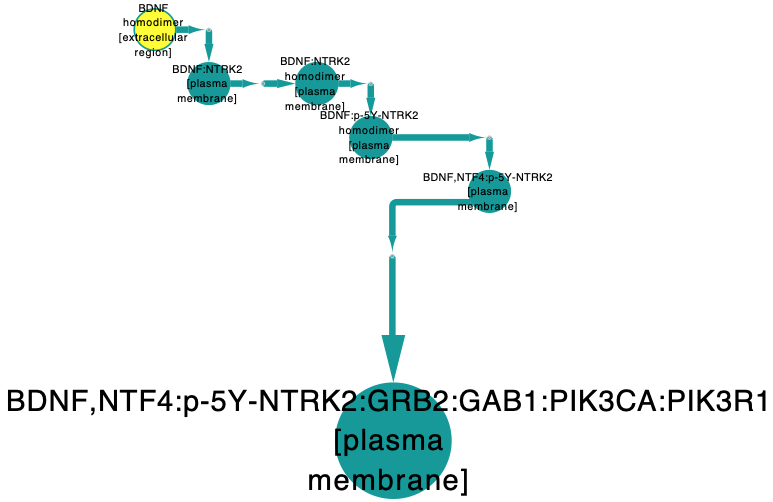
Studying BDNF connection to mTOR



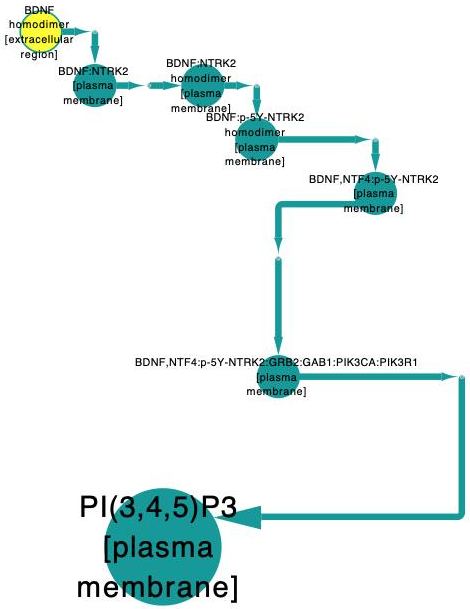
Studying BDNF connection to mTOR



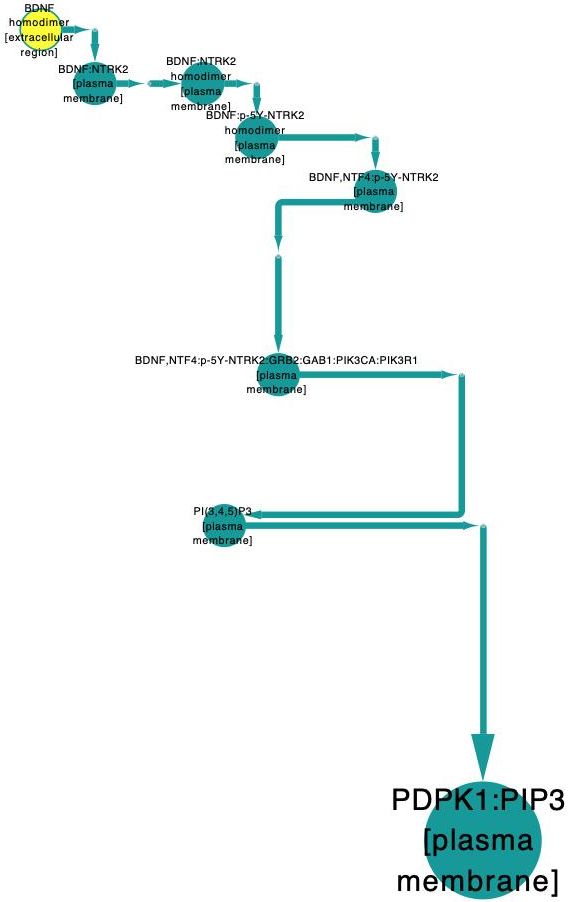
Studying BDNF connection to mTOR



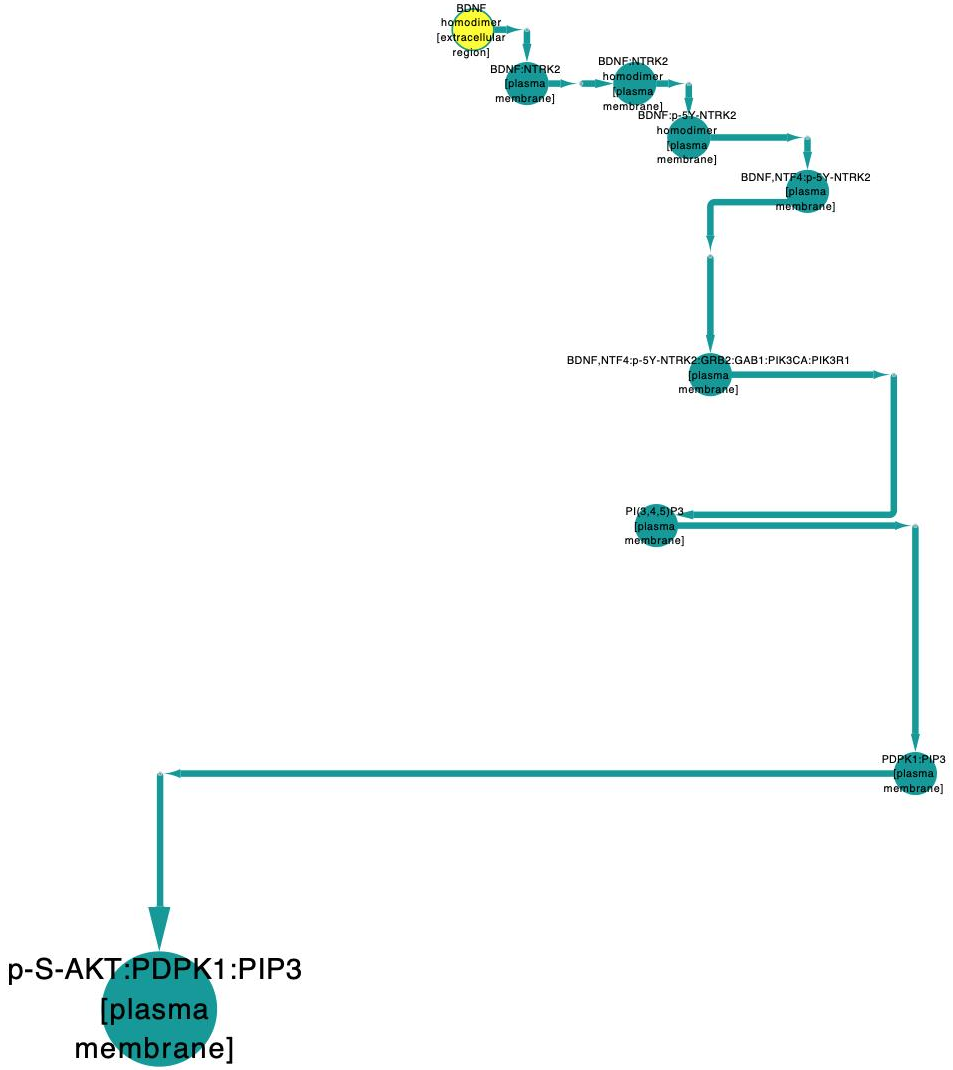
Studying BDNF connection to mTOR



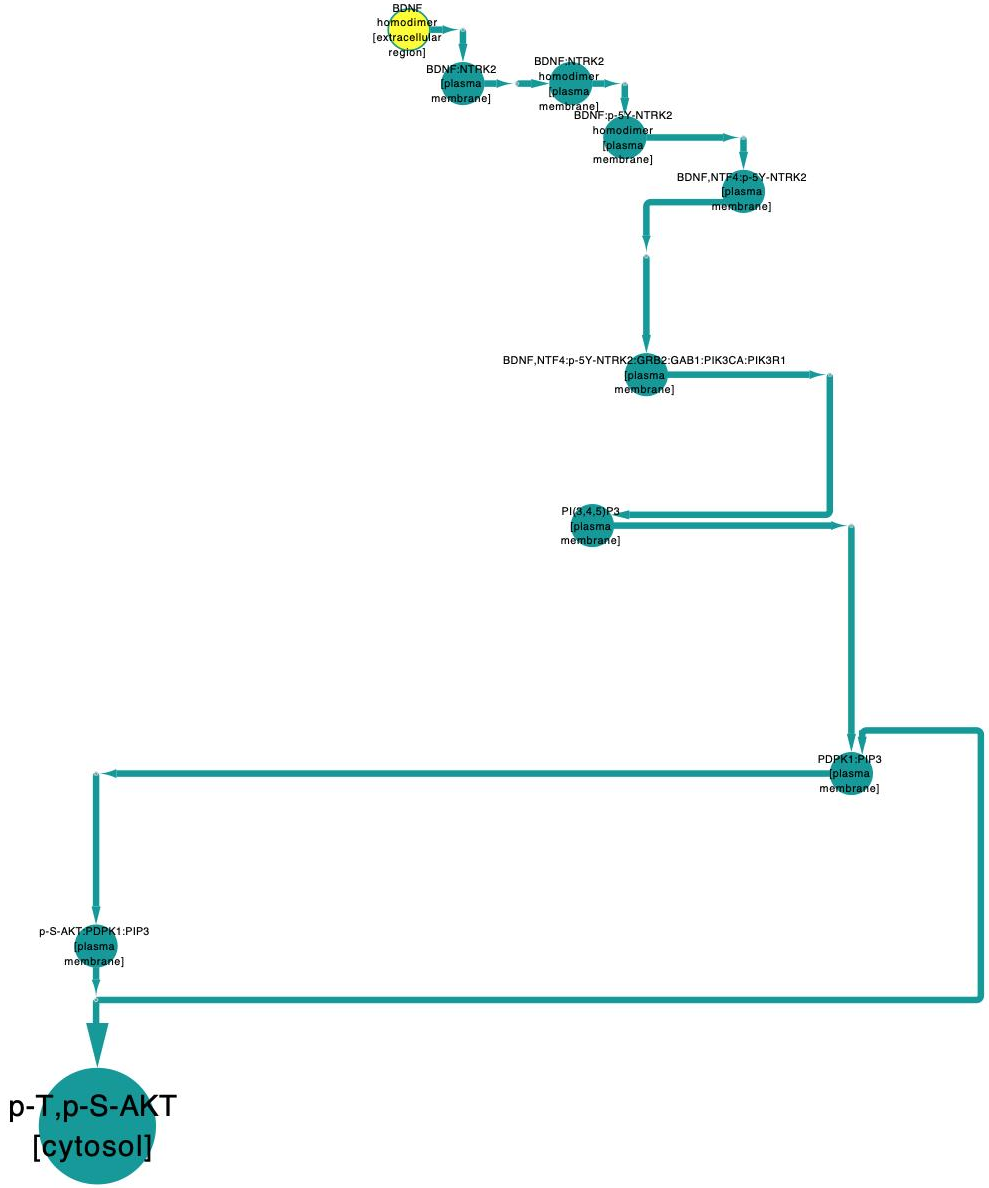
Studying BDNF connection to mTOR



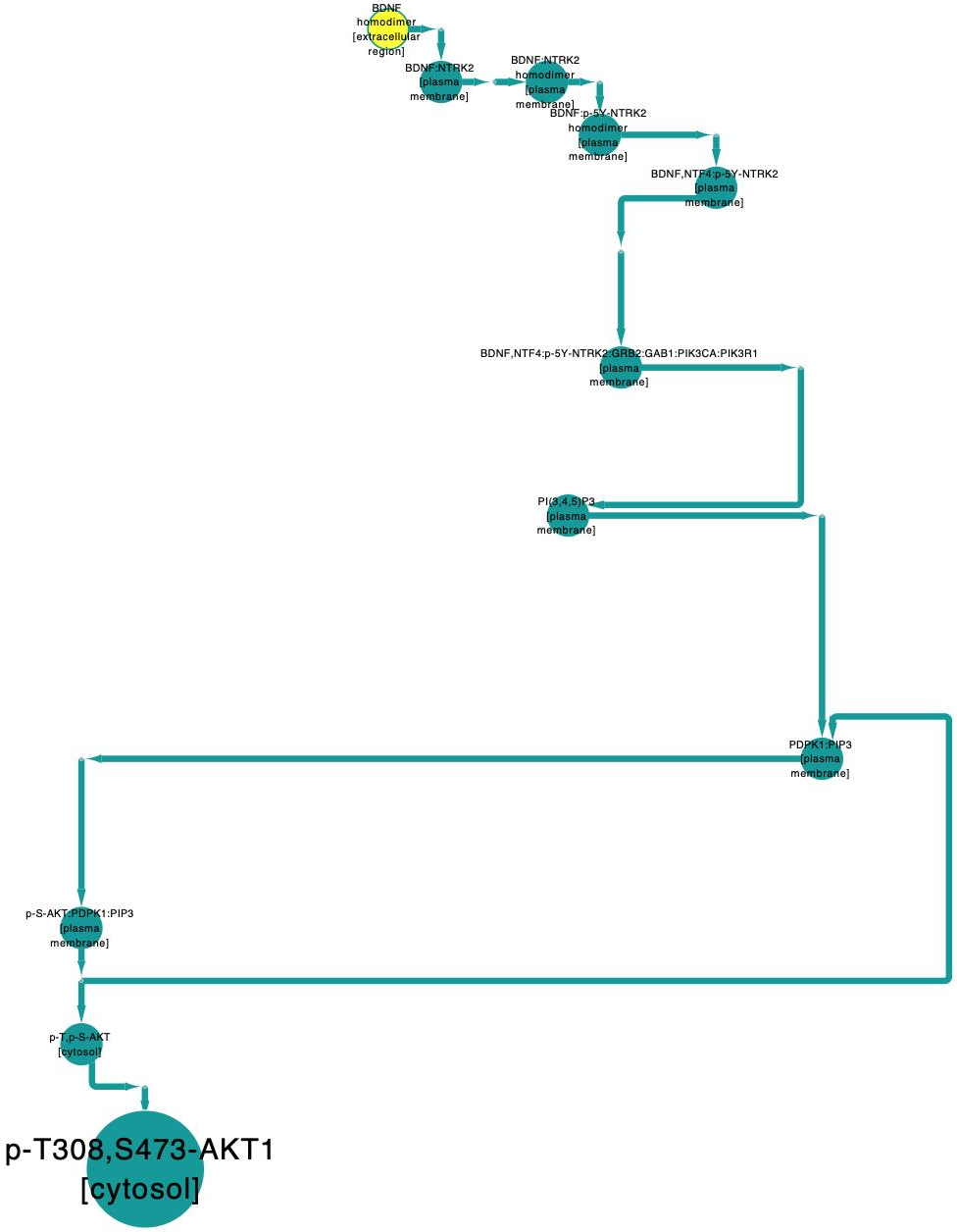
Studying BDNF connection to mTOR



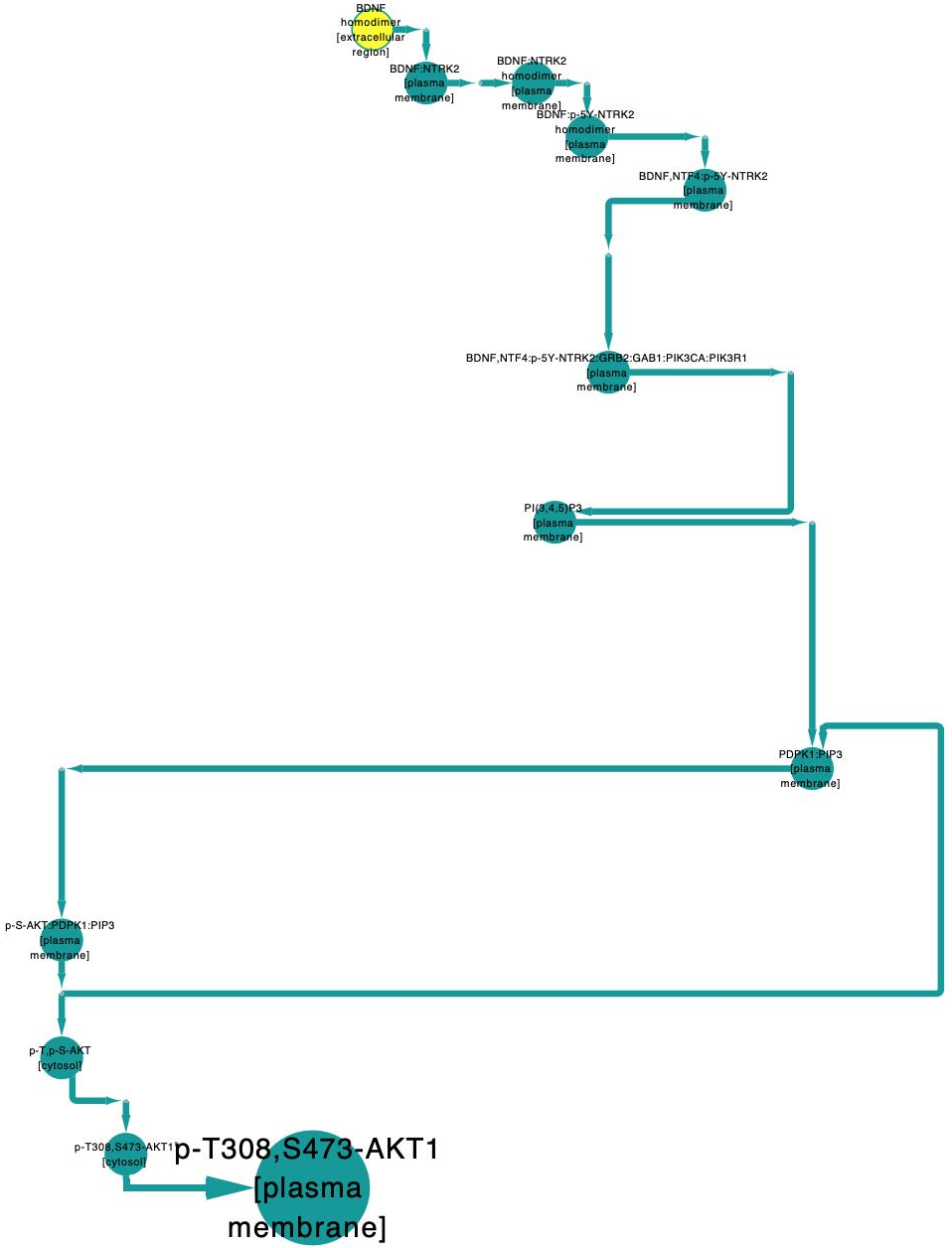
Studying BDNF connection to mTOR



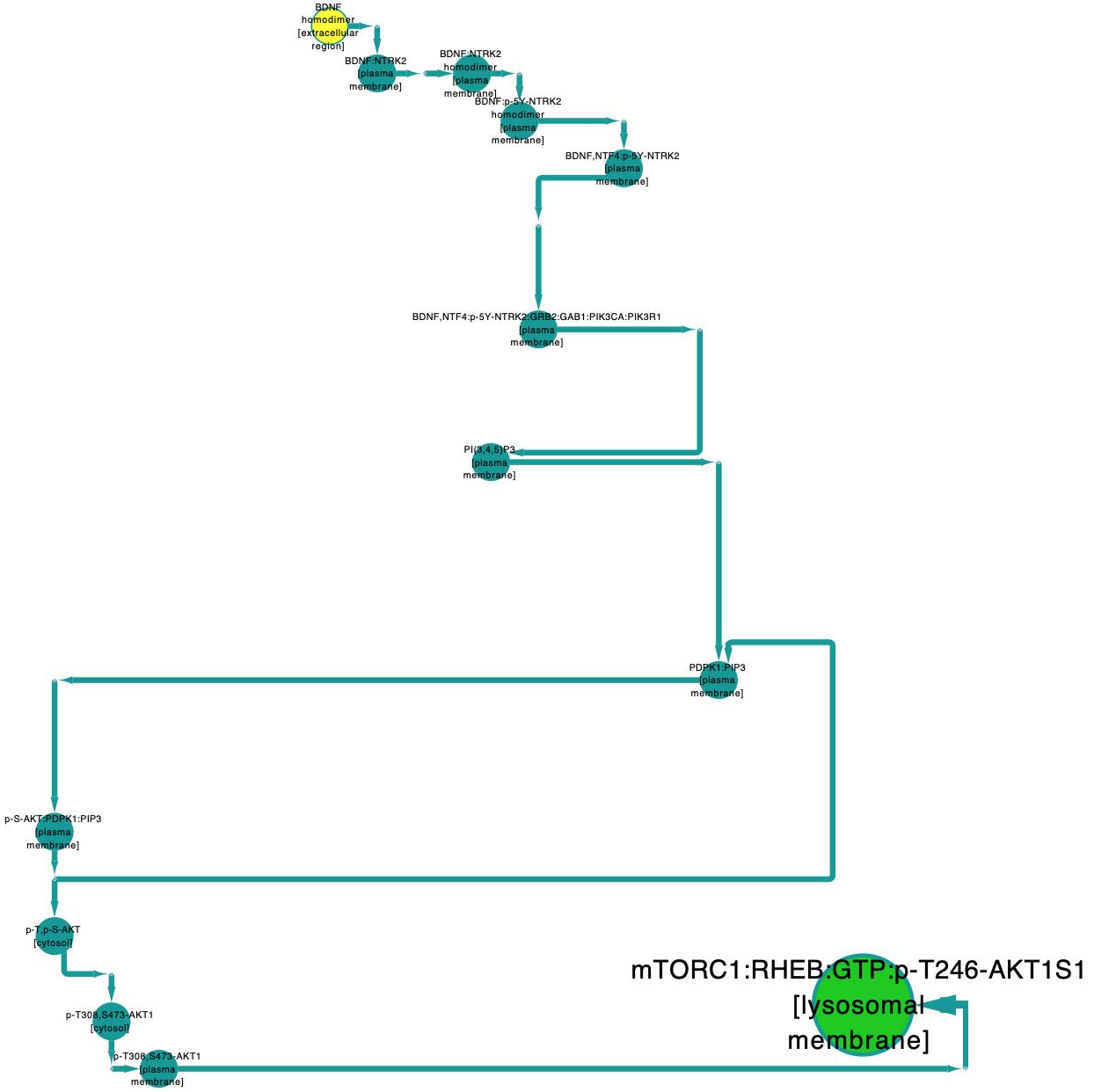
Studying BDNF connection to mTOR



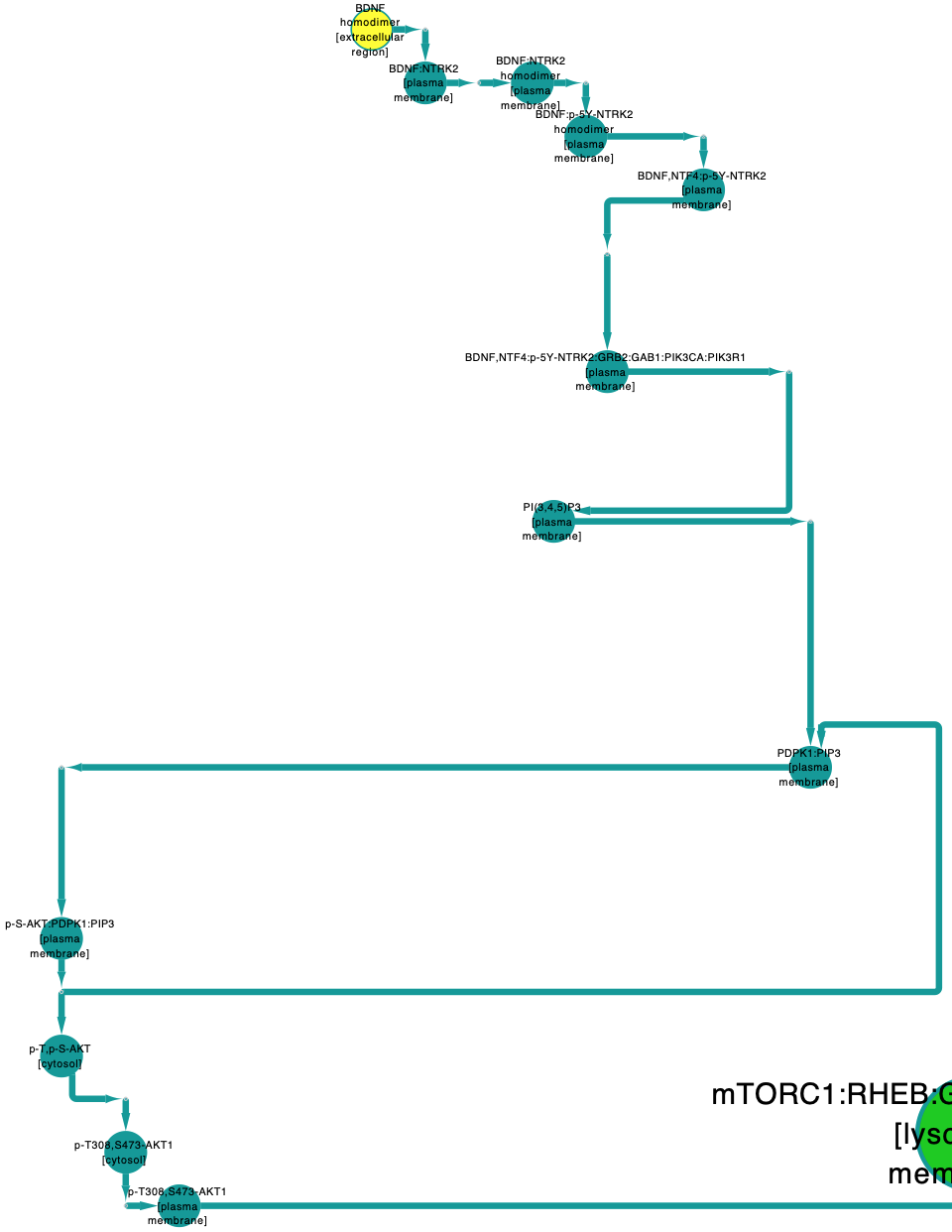
Studying BDNF connection to mTOR

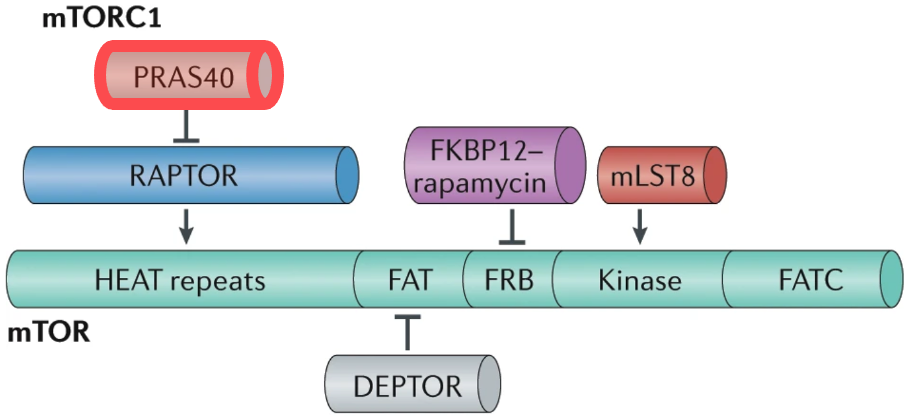


Studying BDNF connection to mTOR



Studying BDNF connection to mTOR

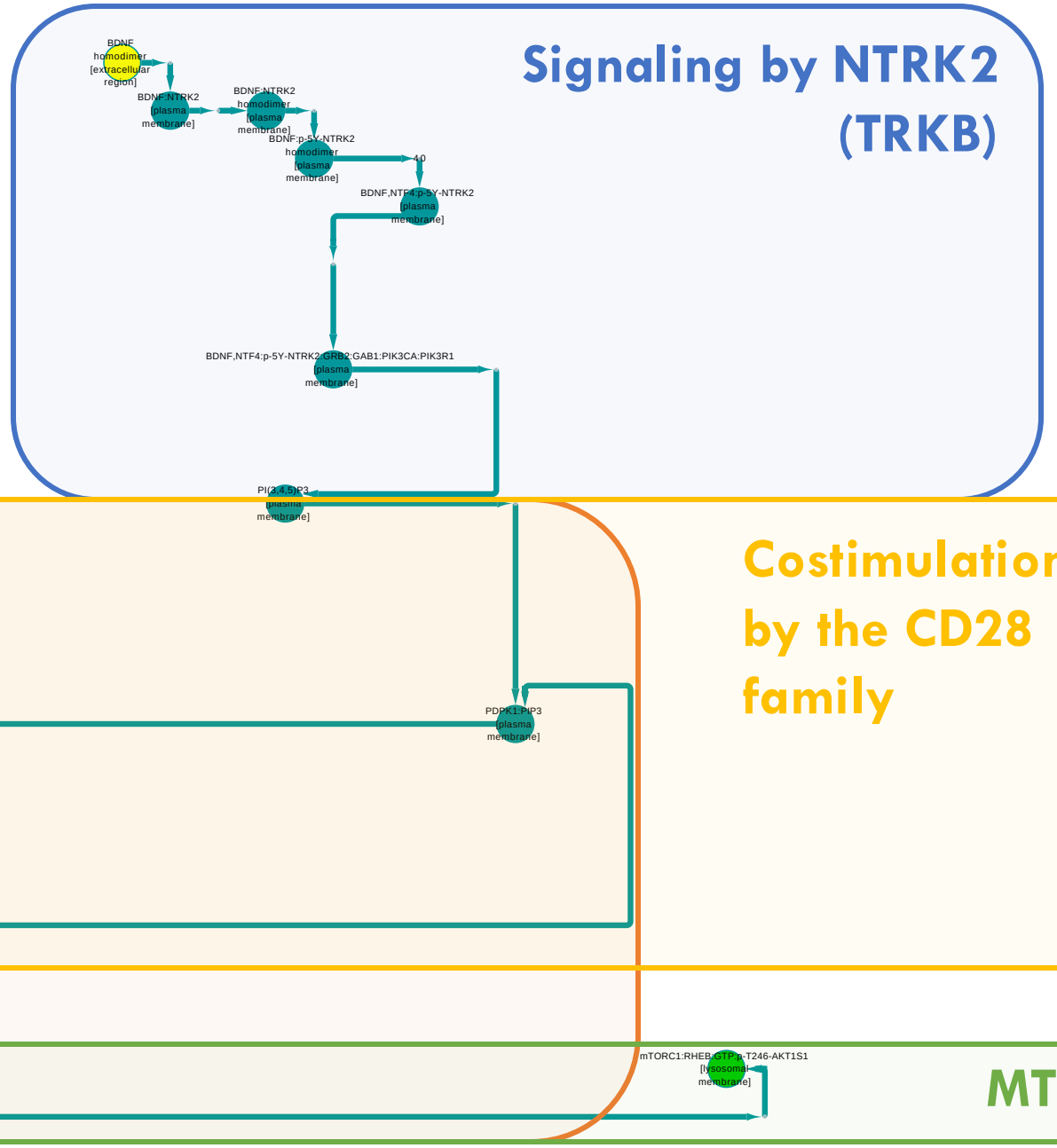




mTORC1:RHEB:GTP:p-T246-AKT1S1 [lysosomal membrane]

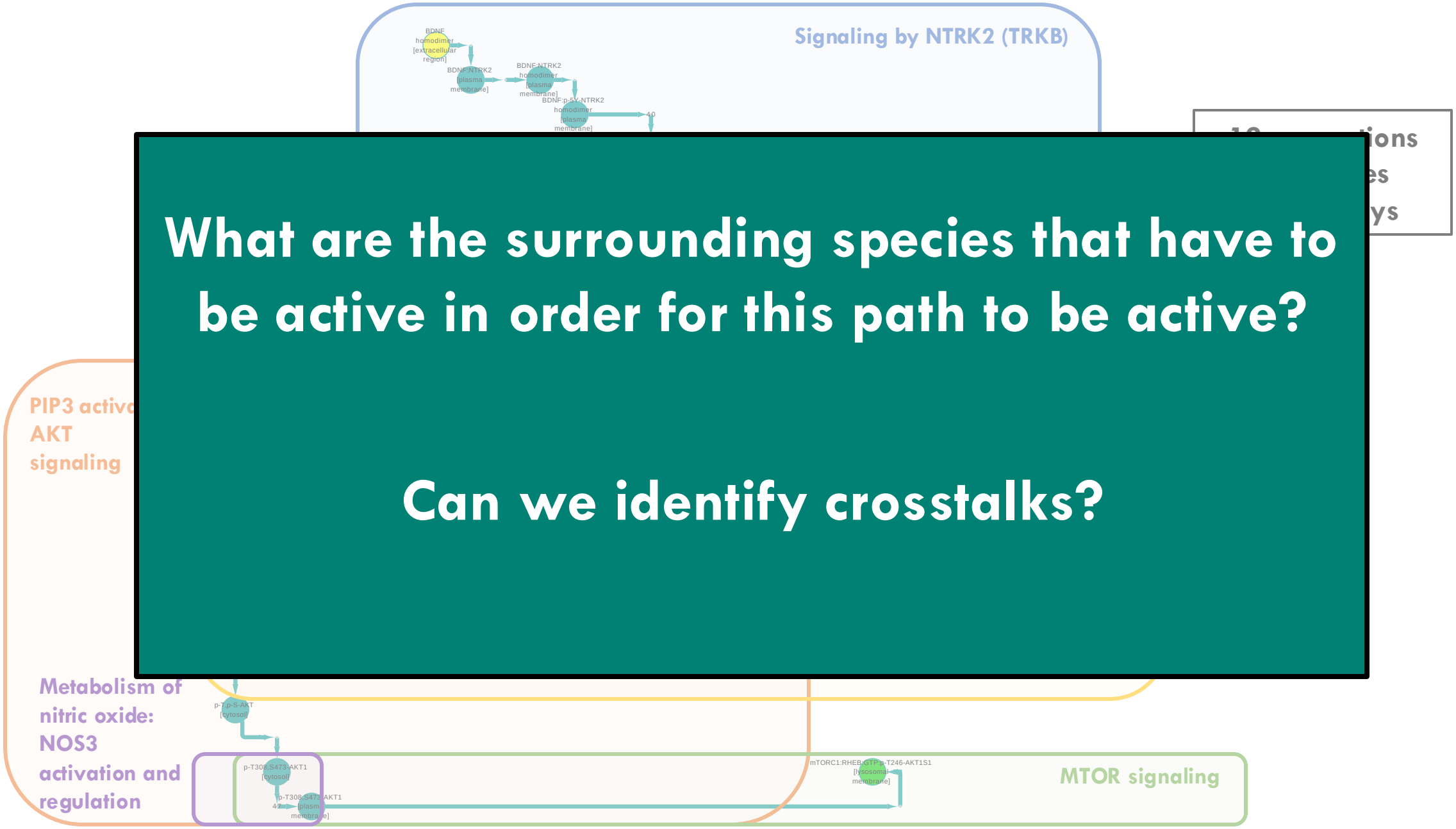
Activated Akt1 phosphorylates PRAS40

Studying BDNF connection to mTOR



12 connections
13 species
5 pathways

Studying BDNF connection to mTOR

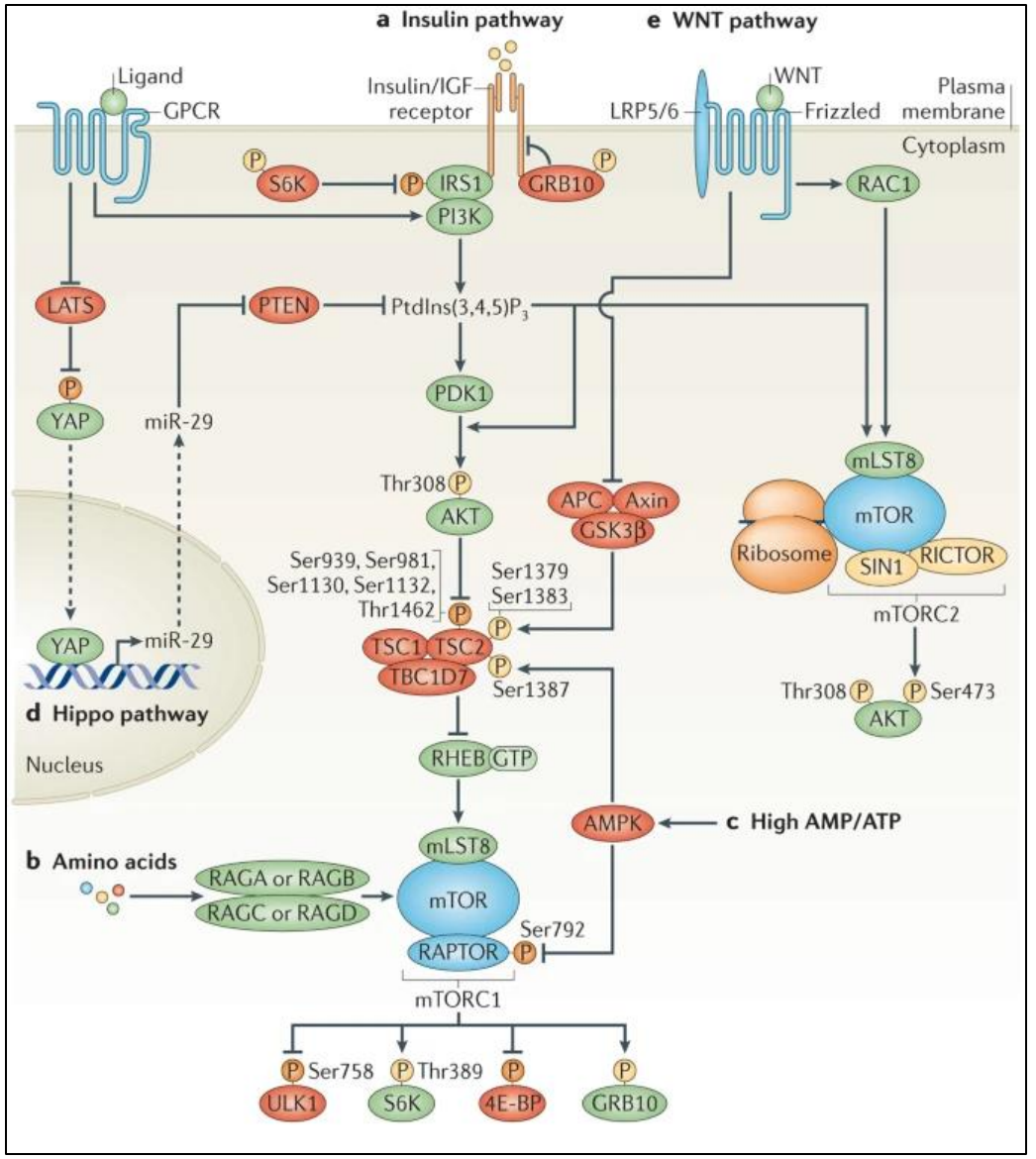


What are the surrounding species that have to be active in order for this path to be active?

Can we identify crosstalks?

Crosstalks in signaling pathways

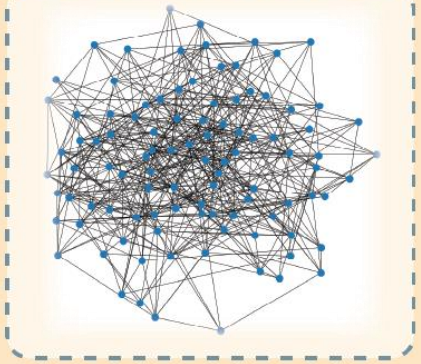
Heinrichs, Arianne. "Signalling Crosstalk." *Nature Reviews Molecular Cell Biology*, 2006



Shimobayashi, Mitsugu, and Michael N. Hall. "Making New Contacts: The MTOR Network in Metabolism and Signalling Crosstalk." *Nature Reviews Molecular Cell Biology*, 2014

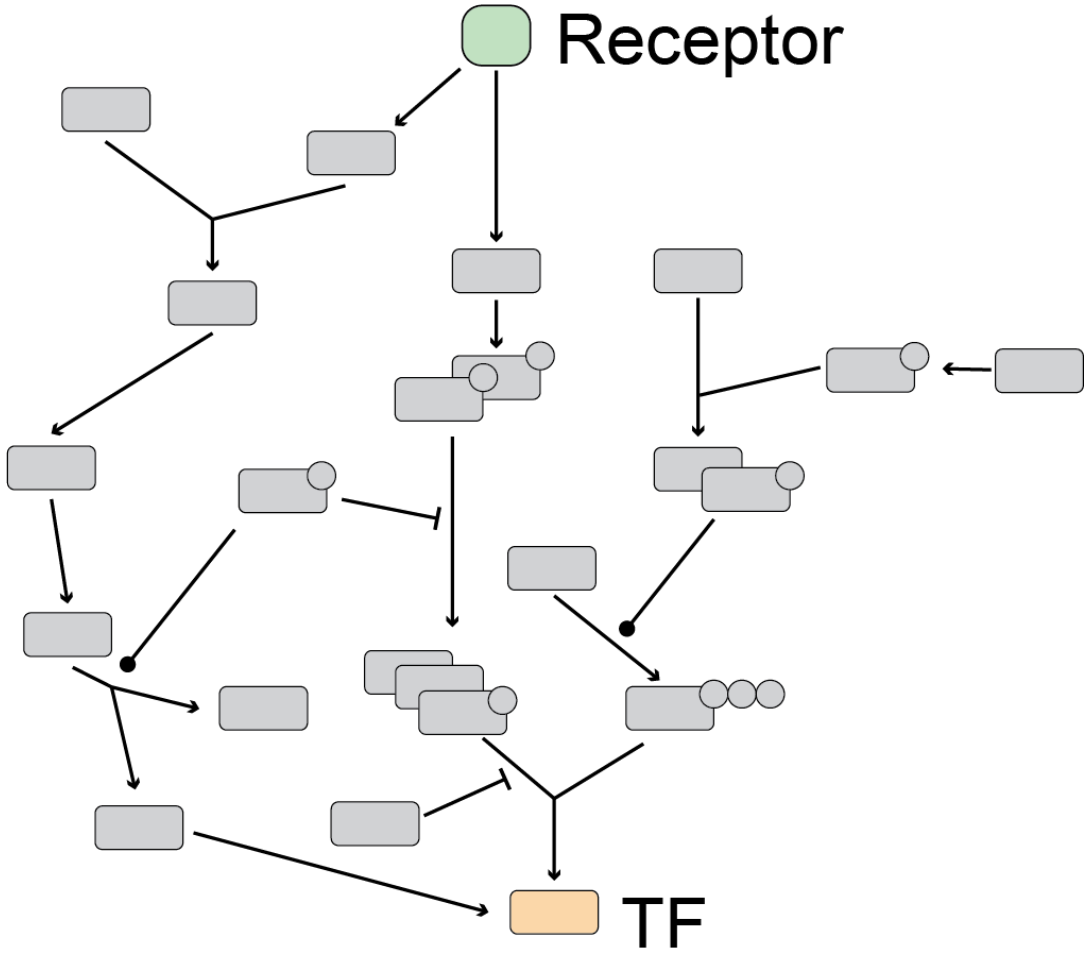
Create balanced signaling networks

SIGMA Method



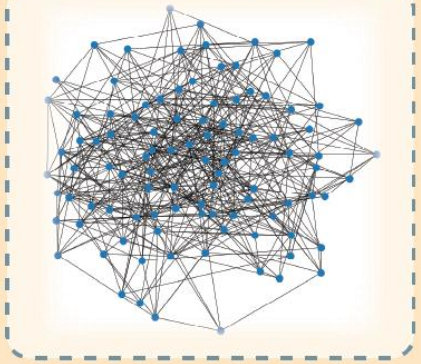
reactome

Signaling network



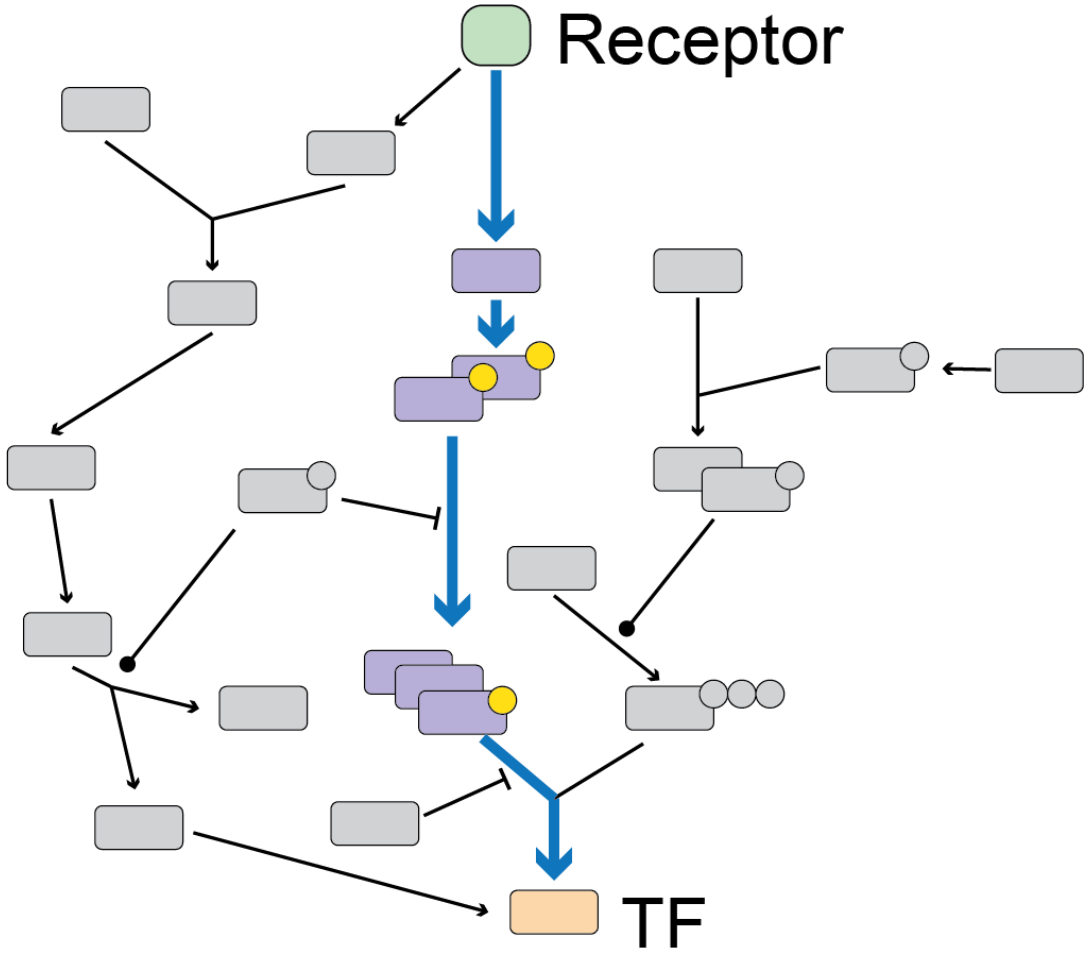
Create balanced signaling networks

SIGMA Method



reactome

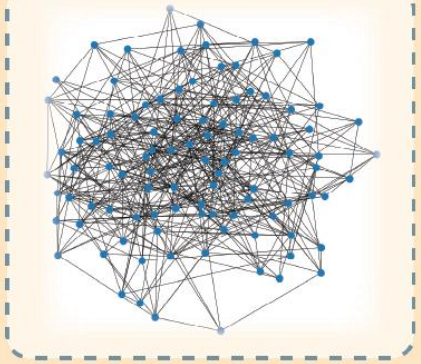
Signaling network



minimal path

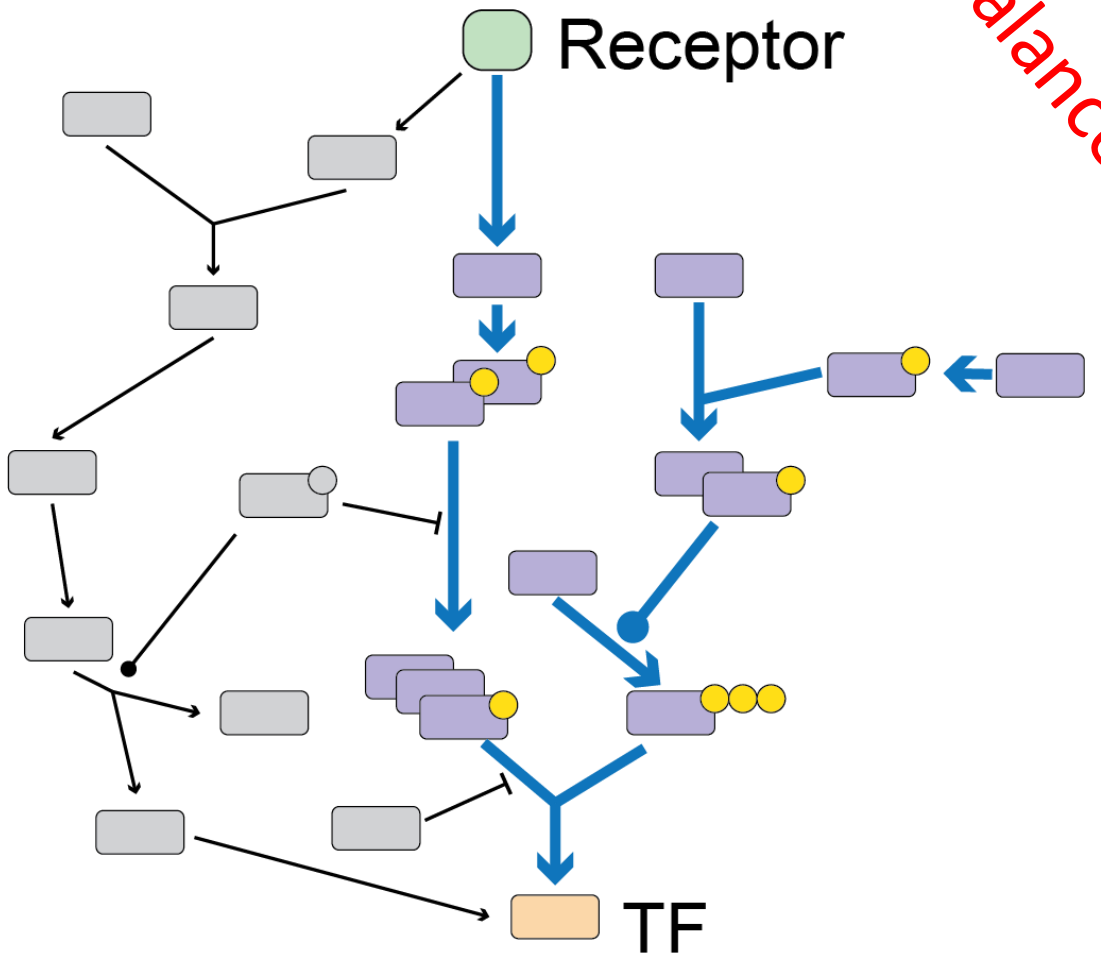
Create balanced signaling networks

SIGMA Method



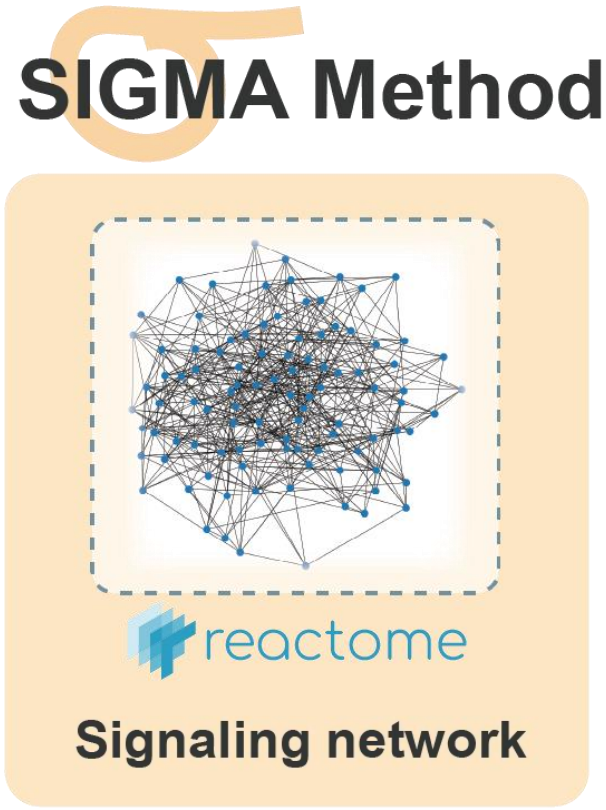
reactome

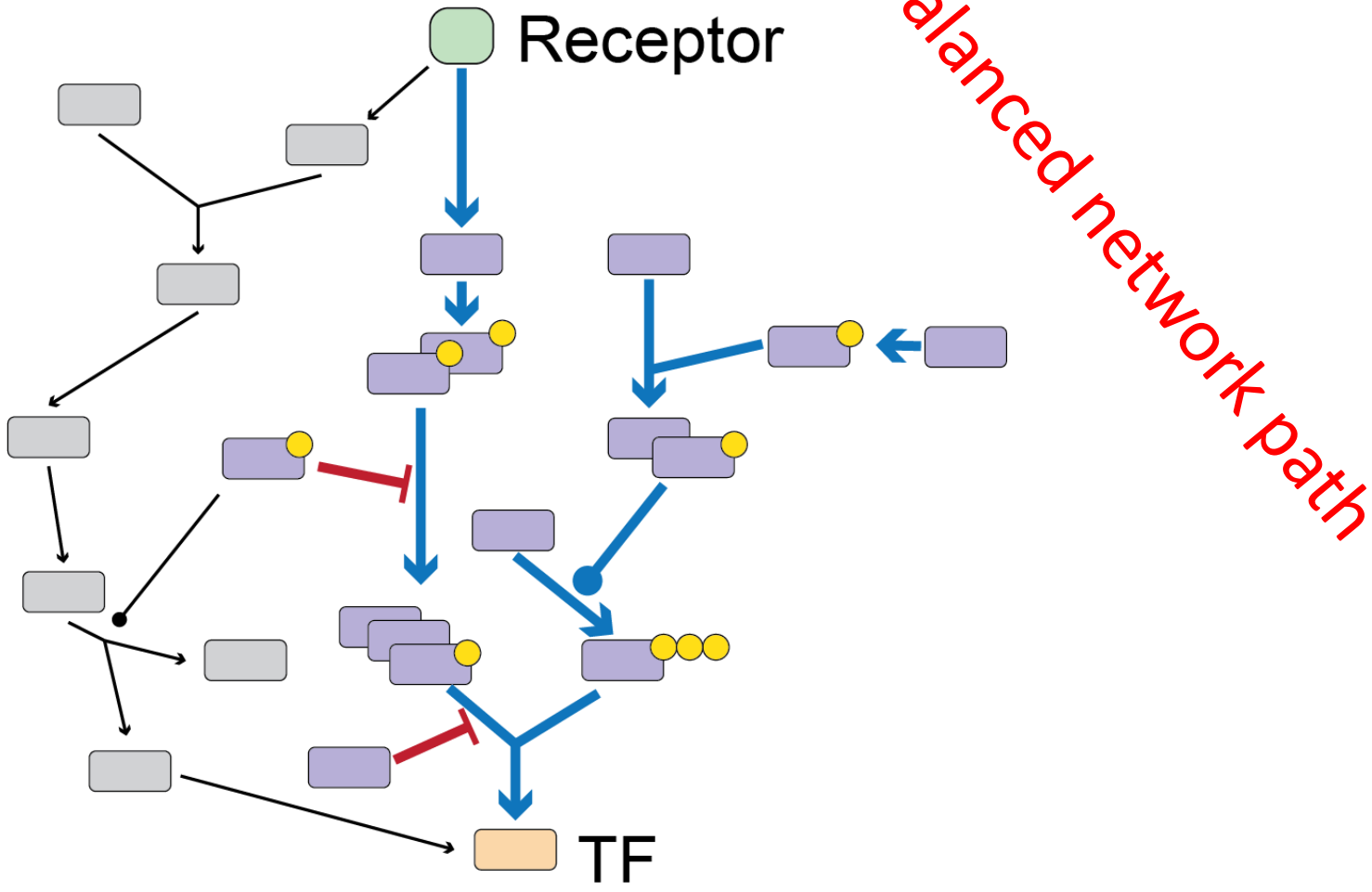
Signaling network



balanced network path

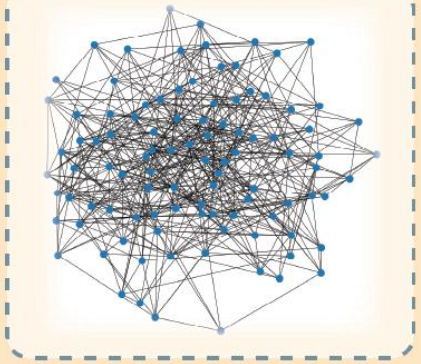
Create balanced signaling networks





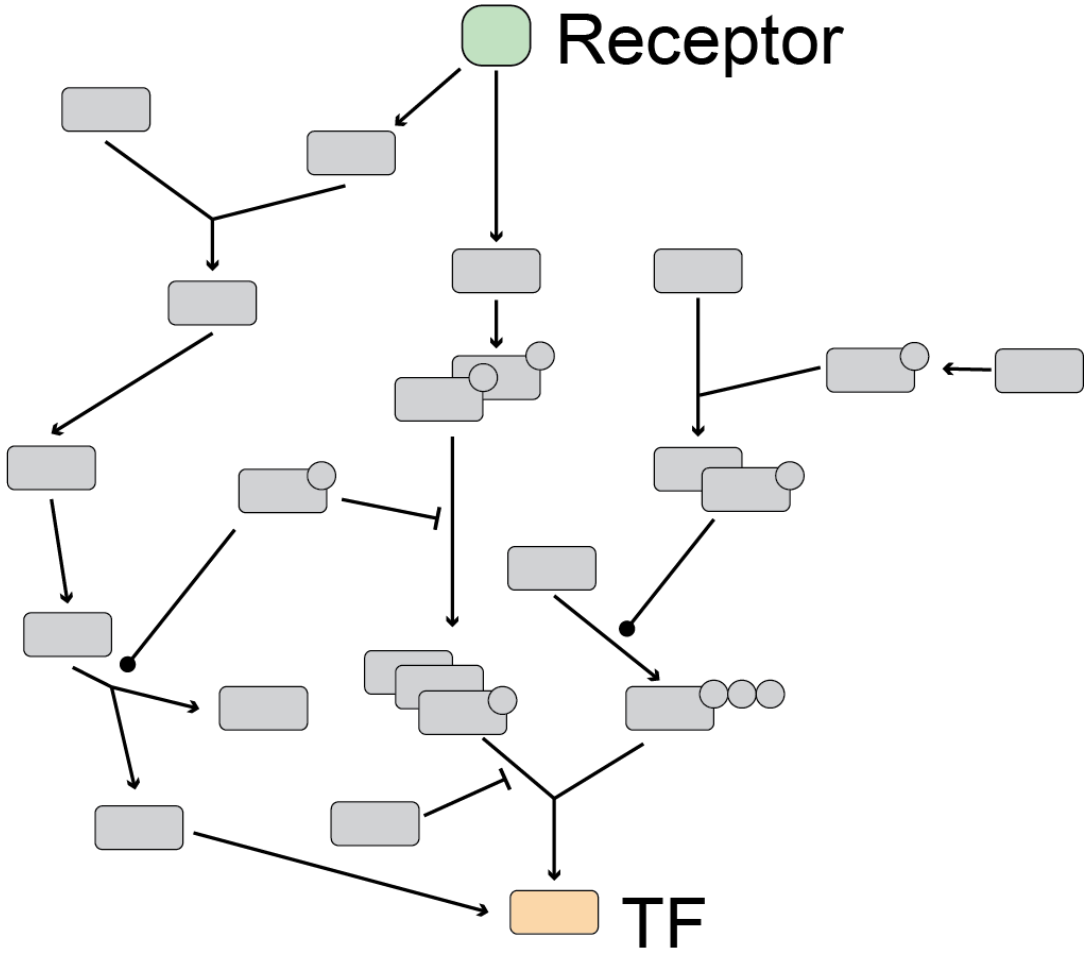
Create balanced signaling networks

SIGMA Method



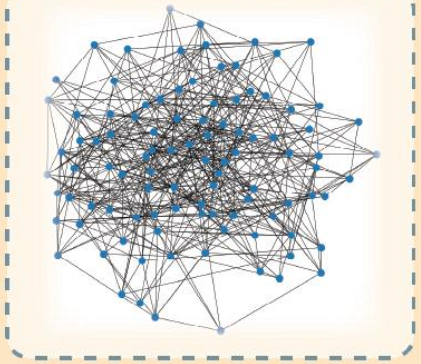
reactome

Signaling network



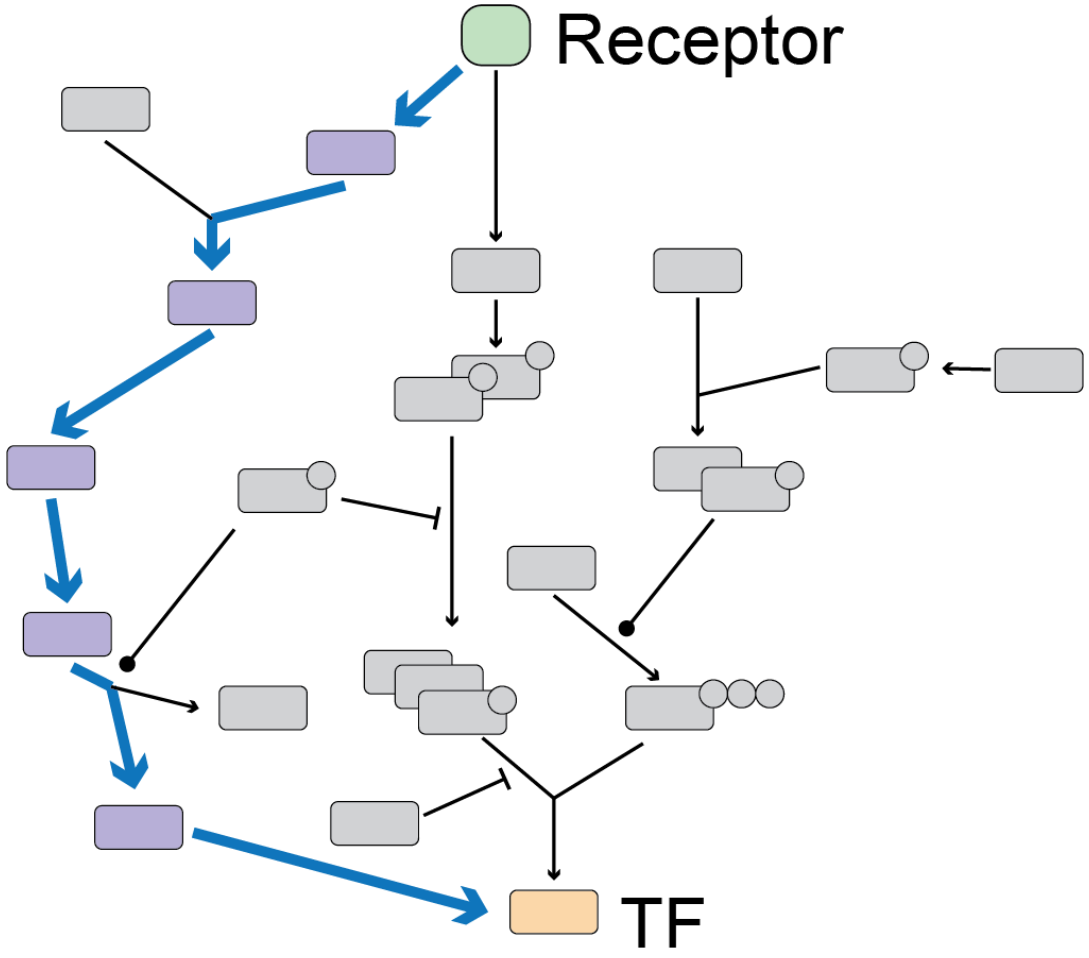
Create balanced signaling networks

SIGMA Method

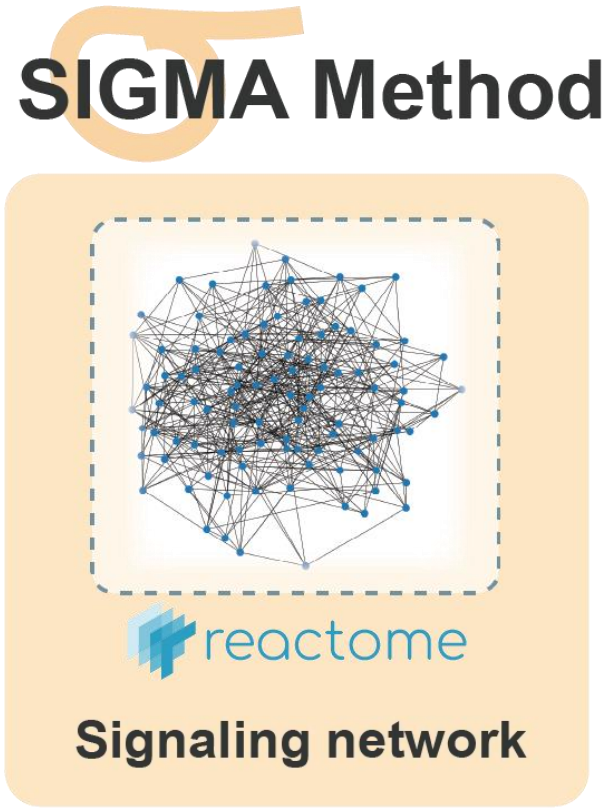


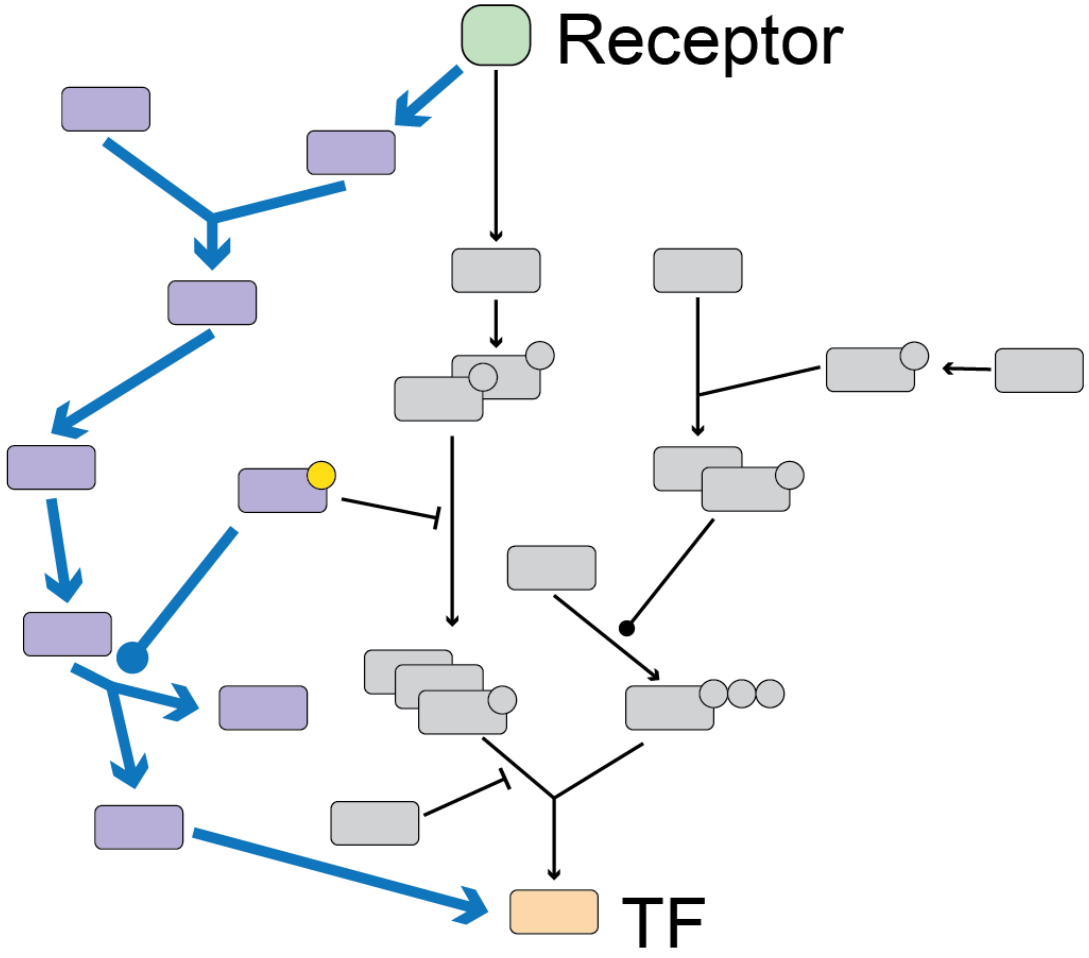
reactome

Signaling network



Create balanced signaling networks

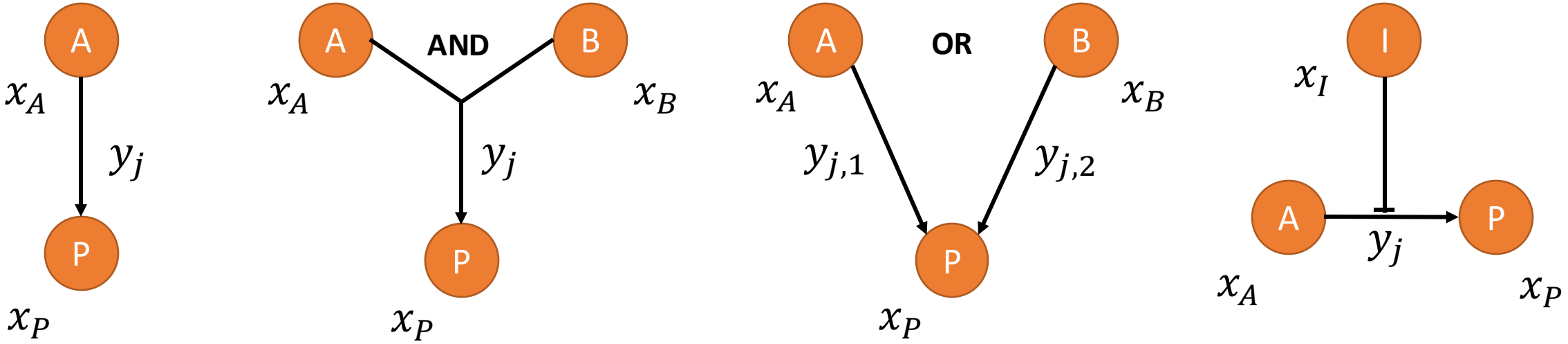




Method for generating balanced signaling networks

From species connections to reactions

- It is based on optimizing pathway topology
- The reactant-reaction-product relations are the motifs



Mitsos, Alexander, et al. "Identifying Drug Effects via Pathway Alterations Using an Integer Linear Programming Optimization Formulation on Phosphoproteomic Data." *PLOS Computational Biology*, 2009

Method for generating balanced signaling networks

A hybrid sequential method

1) PathTracer algorithm to identify the minimal path between two species.

Biotechnology Journal
www.biotechnology-journal.com

Biotechnol. J. 2016, 11, 648–661

Research Article

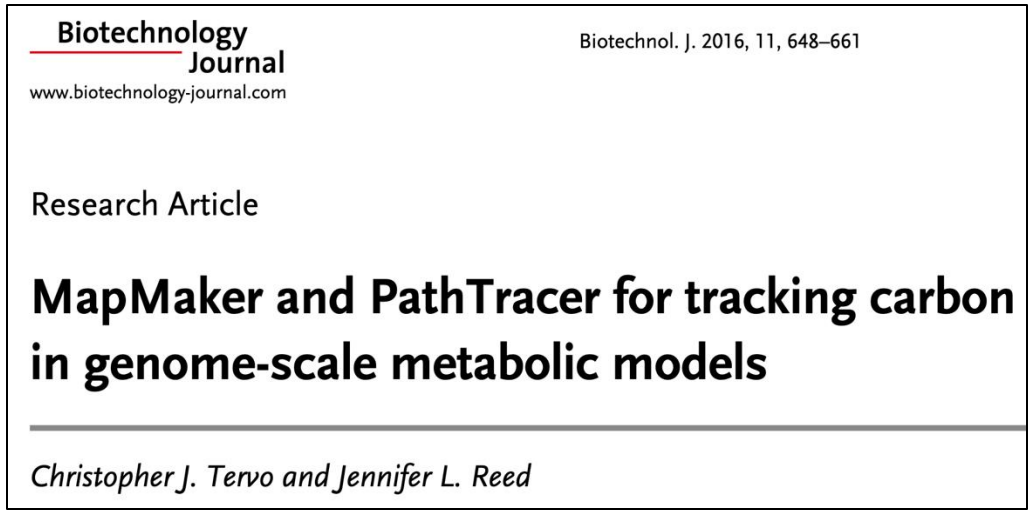
MapMaker and PathTracer for tracking carbon in genome-scale metabolic models

Christopher J. Tervo and Jennifer L. Reed

Method for generating balanced signaling networks

A hybrid sequential method

1) PathTracer algorithm to identify the minimal path between two species.



Biotechnology Journal
www.biotechnology-journal.com

Biotechnol. J. 2016, 11, 648–661

Research Article

MapMaker and PathTracer for tracking carbon in genome-scale metabolic models

Christopher J. Tervo and Jennifer L. Reed

2) Oftadeh et al. formulation of the Mitsos et al. method to identify the minimal network that balances the minimal path.

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

Identifying Drug Effects via Pathway Alterations using an Integer Linear Programming Optimization Formulation on Phosphoproteomic Data

Alexander Mitsos[1], Ioannis N. Melas[2], Paraskeuas Siminelakis[2], Aikaterini D. Chairakaki[2], Julio Saez-Rodriguez[3,4], Leonidas G. Alexopoulos[2]*

Journal of Receptors and Signal Transduction
Volume 38, 2018 - Issue 5-6

Research Article

Accounting for robustness in modeling signal transduction responses

Mohammad Omid Oftadeh & Sayed-Amir Marashi

Pages 442-447 | Received 20 Aug 2018, Accepted 25 Dec 2018, Published online: 22 Feb 2019

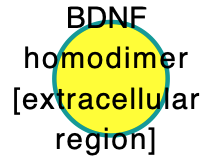
Method for generating balanced signaling networks

Network for minimal path	
Pathways	115
Species	5811
Reactions	8696

From connections to reactions

Network for balanced path	
Pathways	115
Species	5947
Reactions	4409

Studying BDNF connection to mTOR



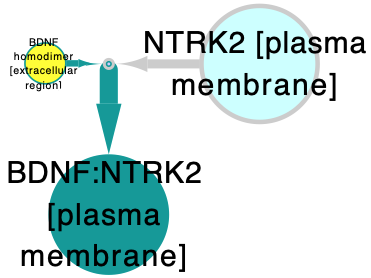
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



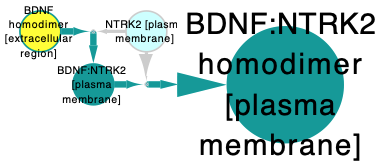
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



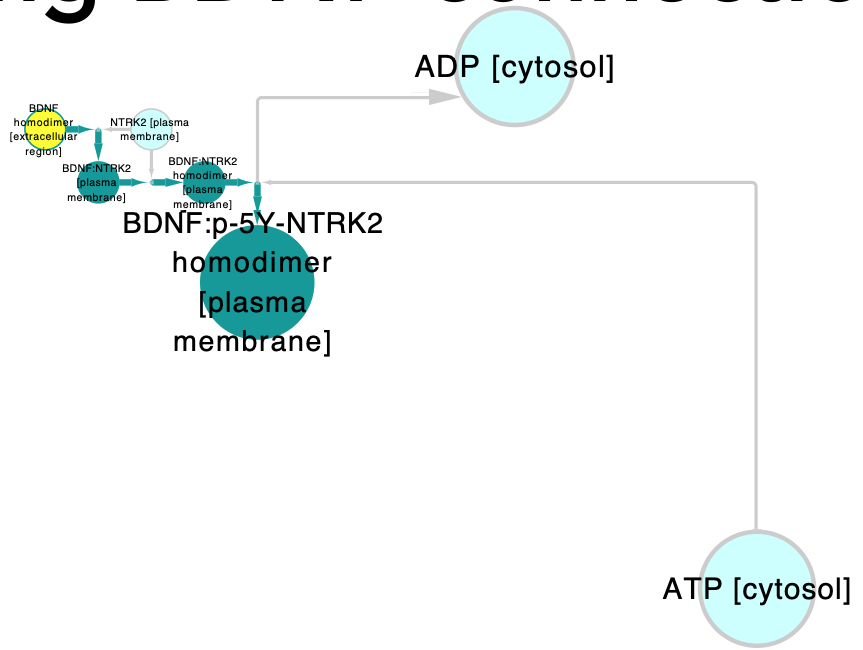
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



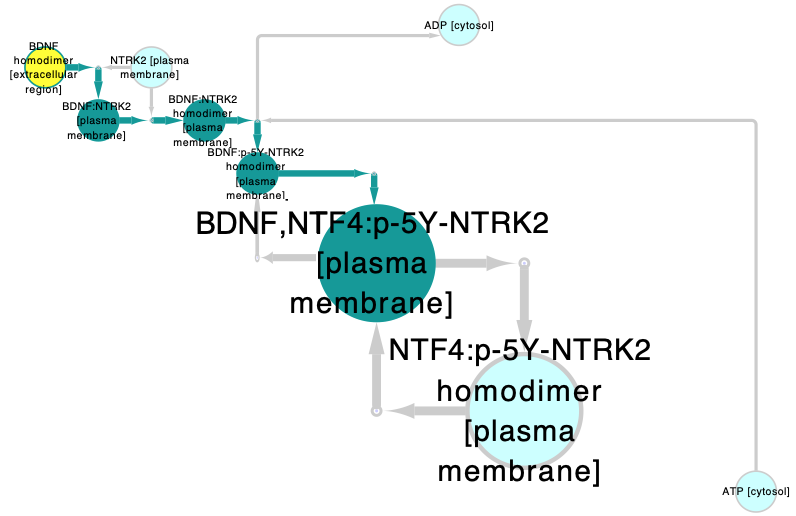
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



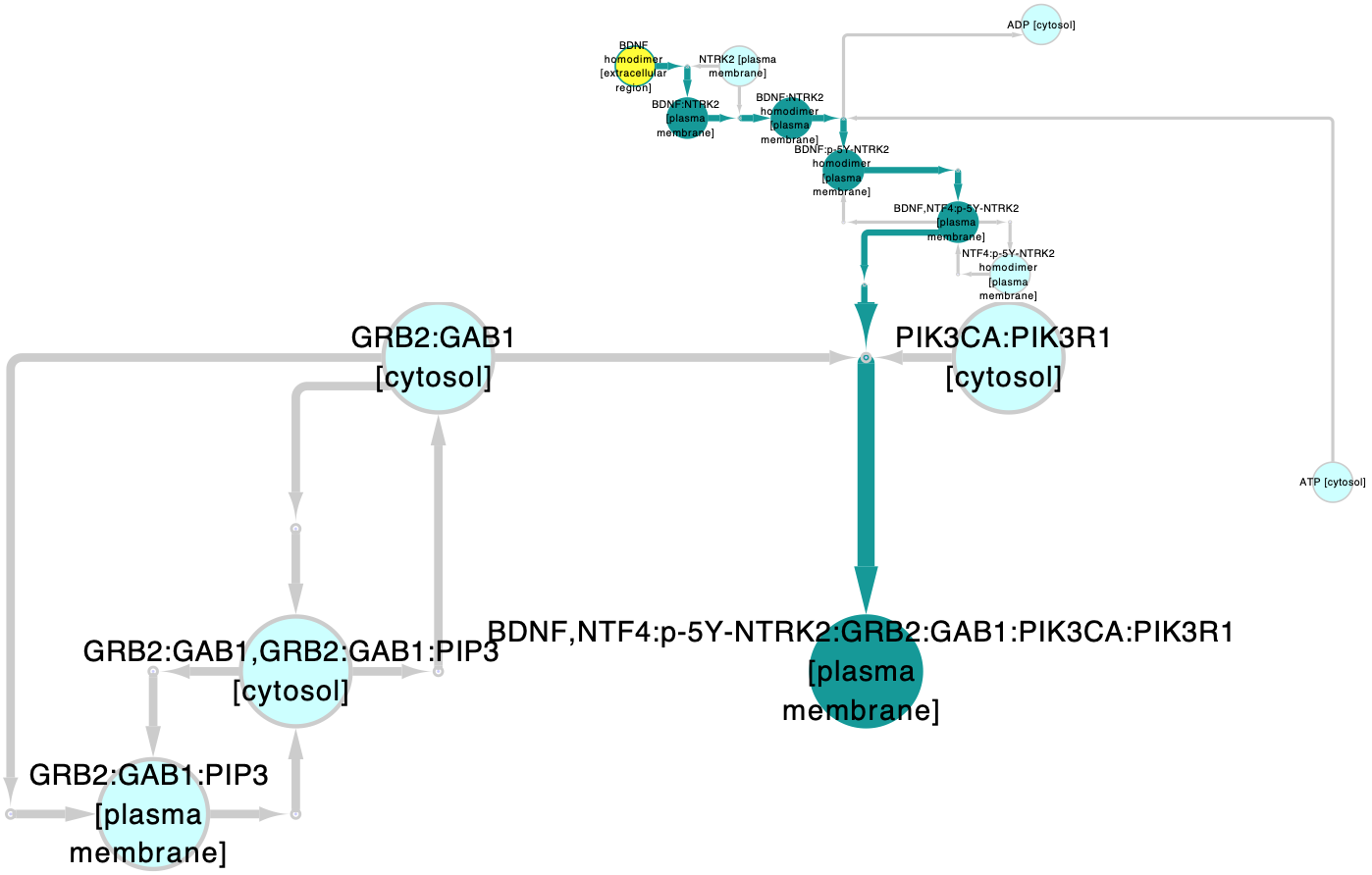
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



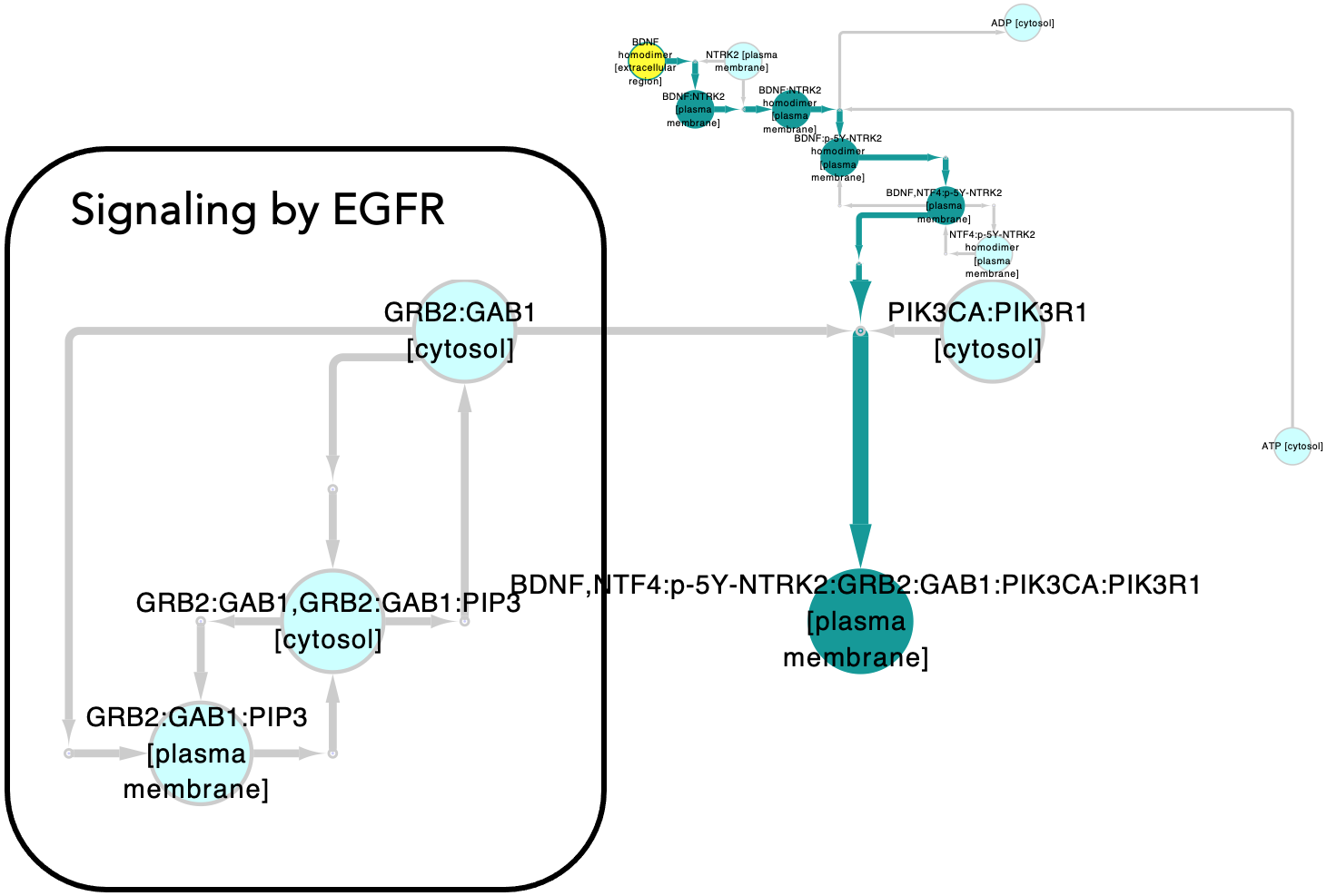
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



Minimal path

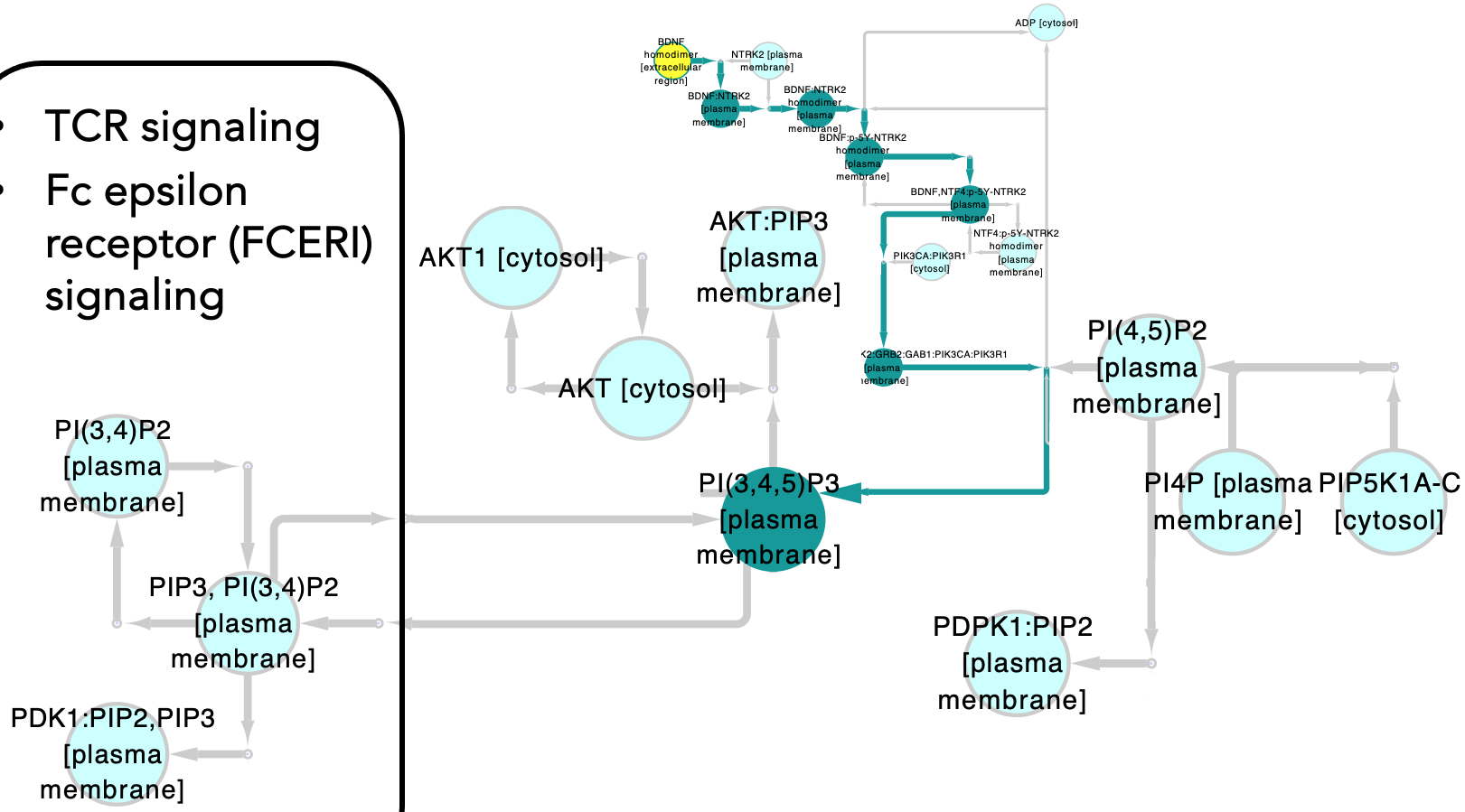
12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR

- TCR signaling
- Fc epsilon receptor (FCERI) signaling



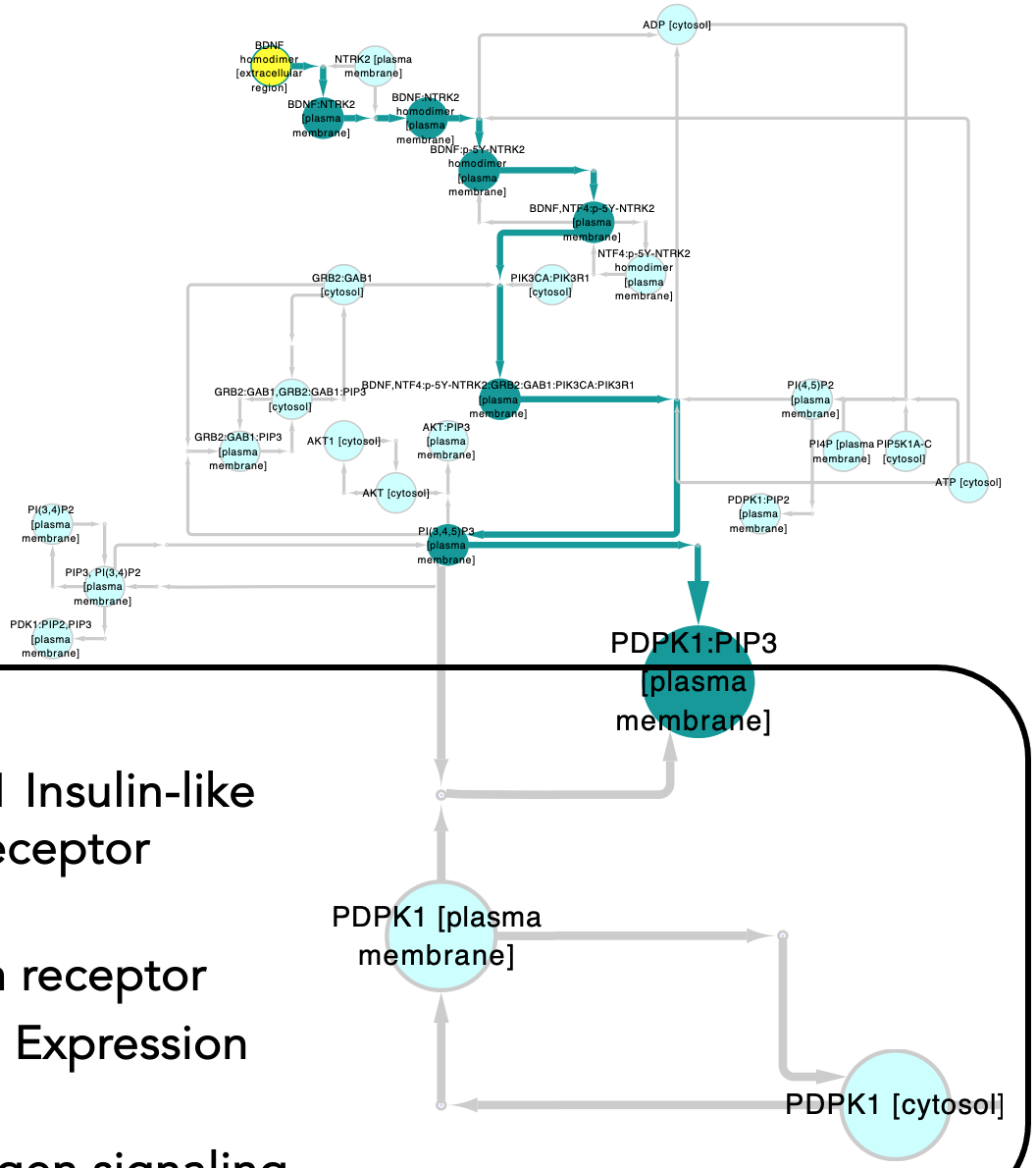
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



- PI3K Cascade
- Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)
- Signaling by Insulin receptor
- Regulation of TP53 Expression and Degradation
- Extra-nuclear estrogen signaling

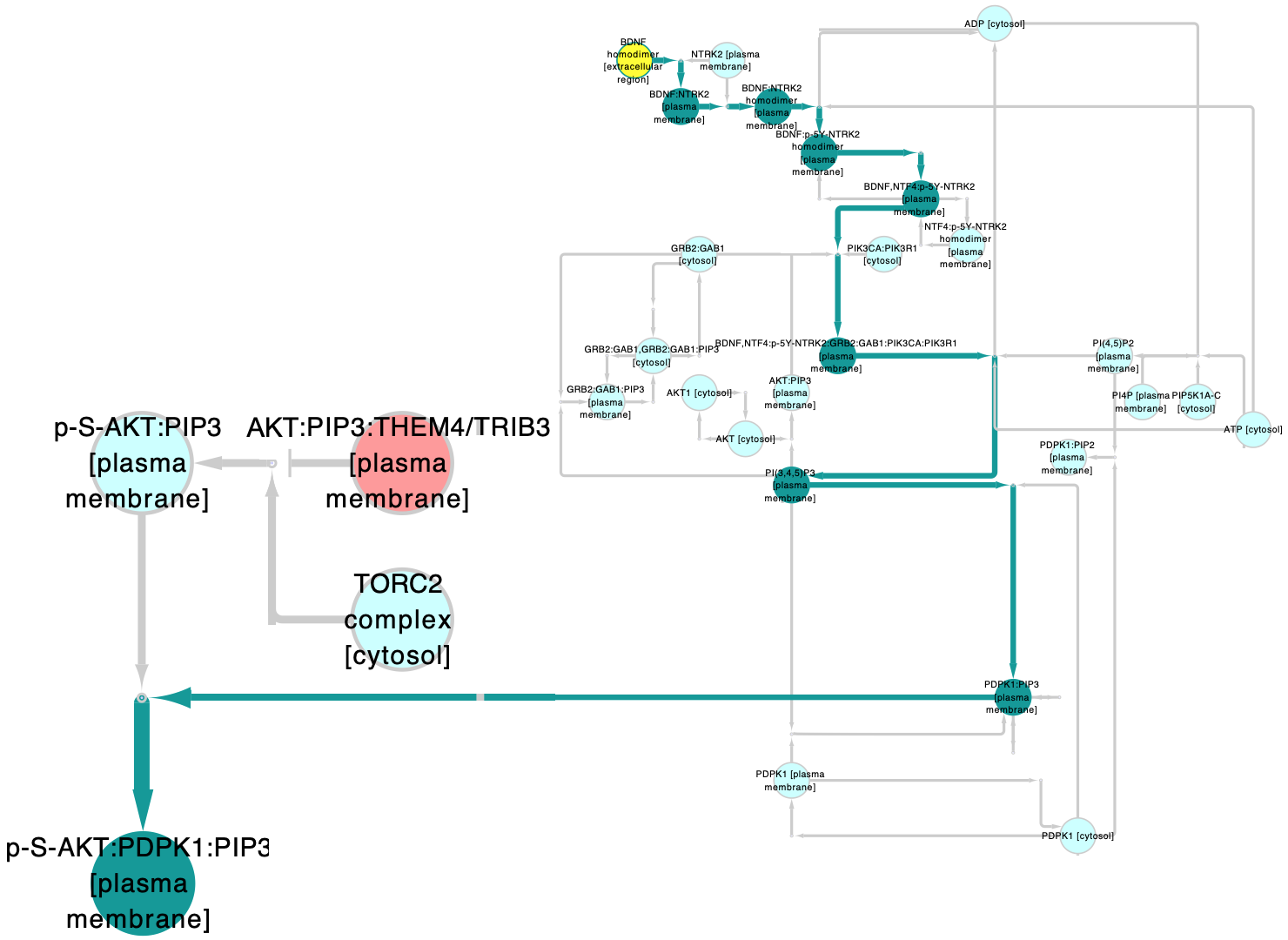
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



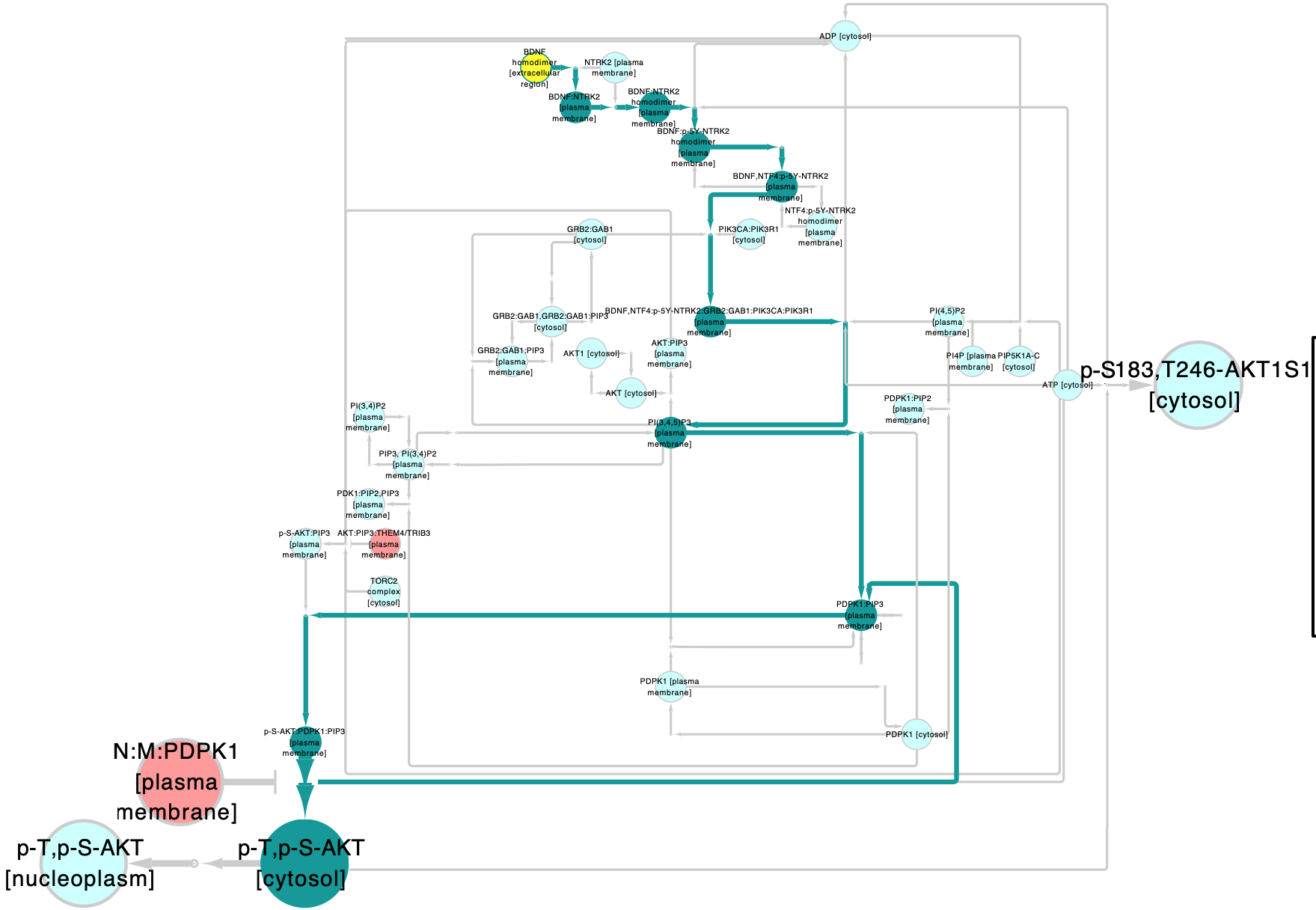
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



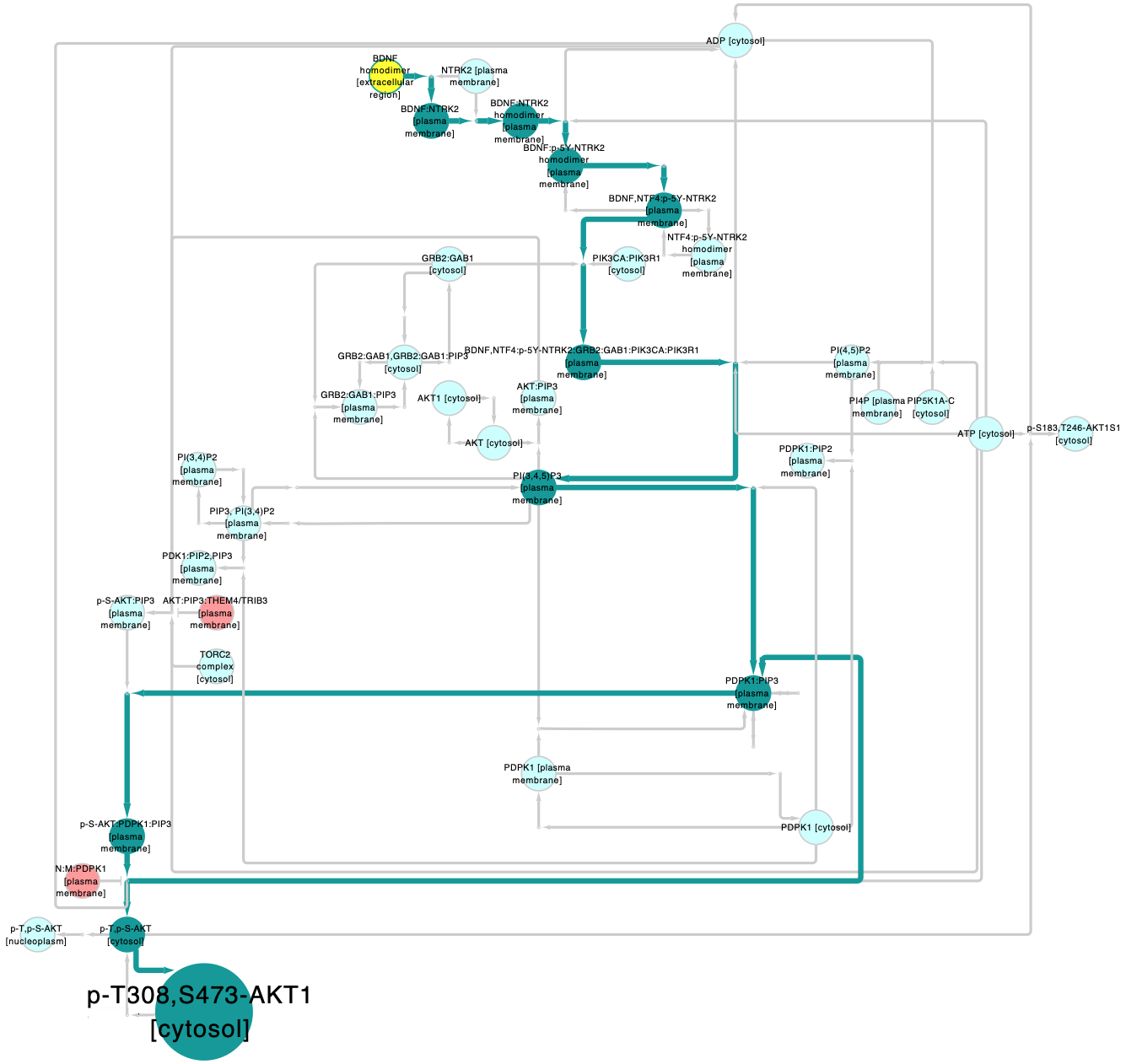
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



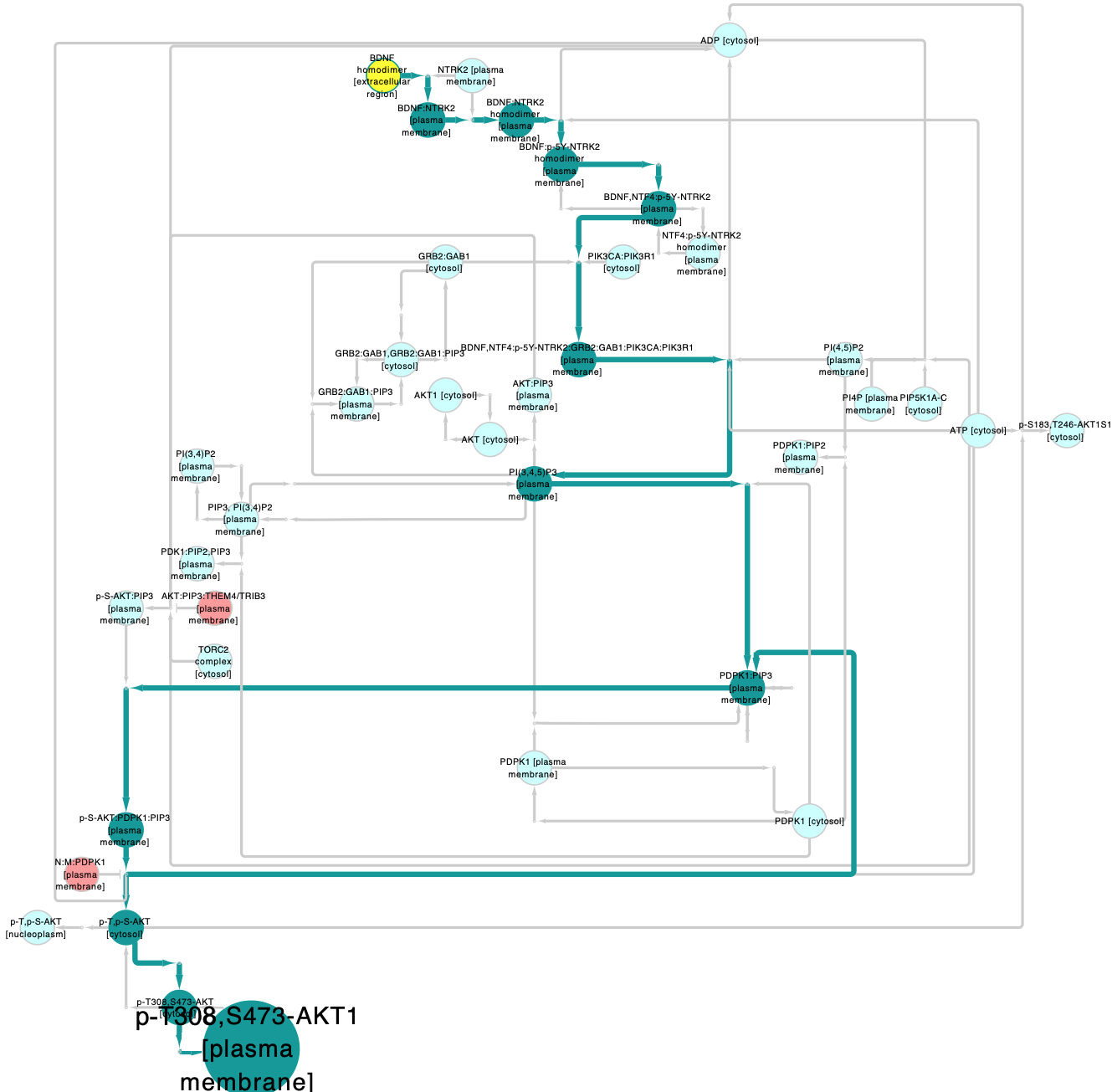
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR



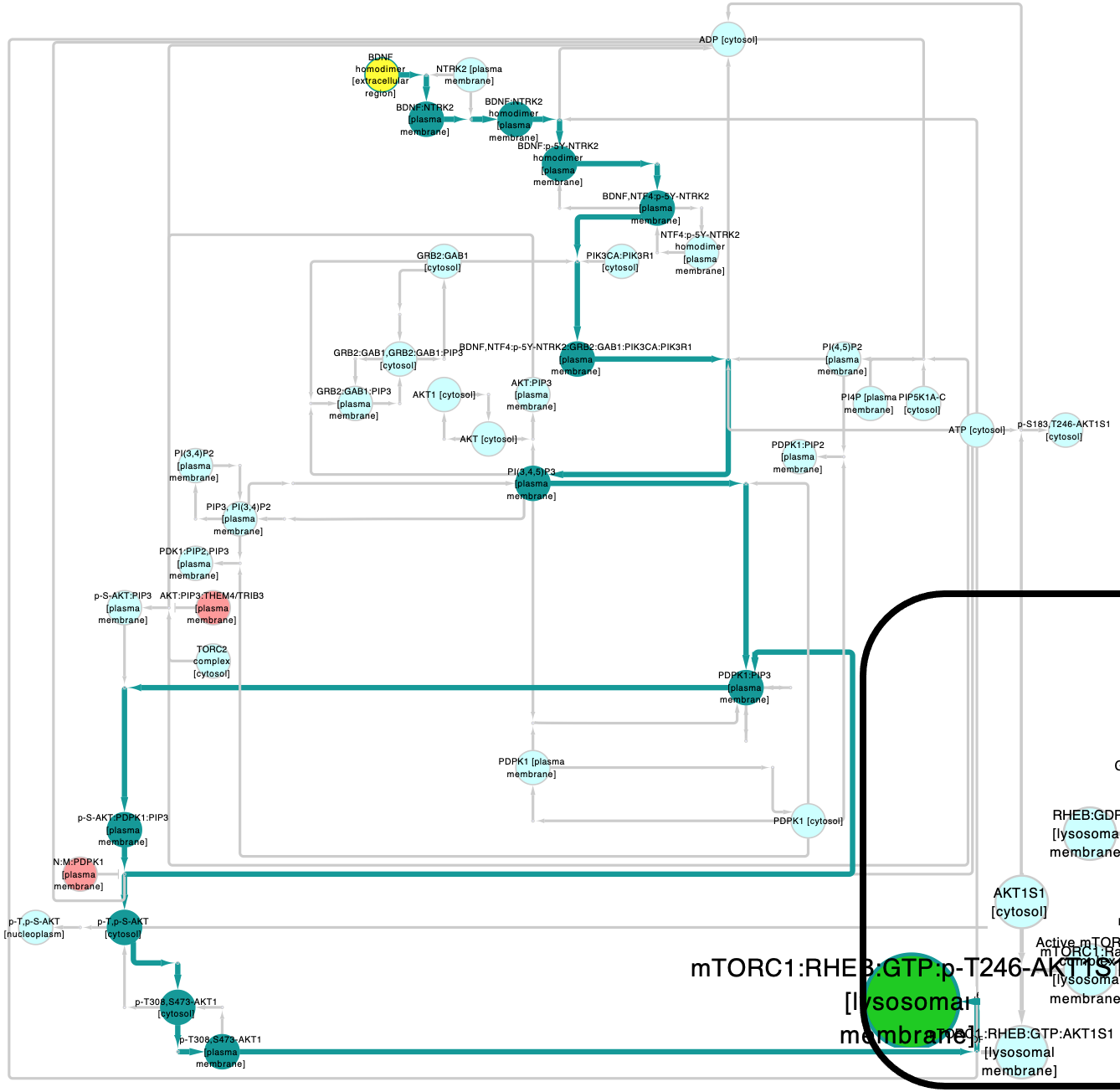
Minimal path

12 connections
13 species
5 pathways

Pathways in minimal path

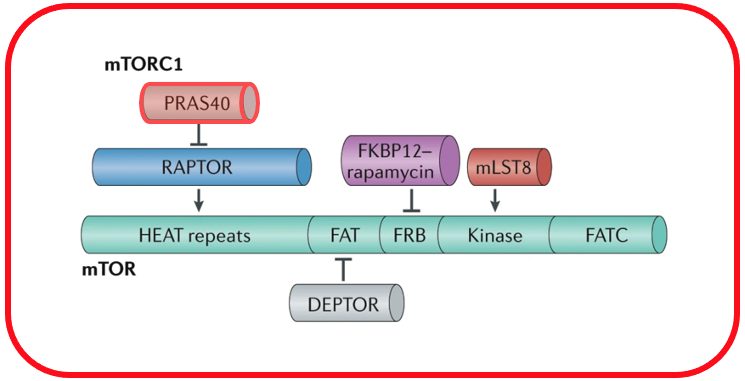
1. Signaling by NTRK2 (TRKB)
2. PIP3 activates AKT signaling
3. Costimulation by the CD28 family
4. Metabolism of nitric oxide: NOS3 activation and regulation
5. MTOR signaling

Studying BDNF connection to mTOR

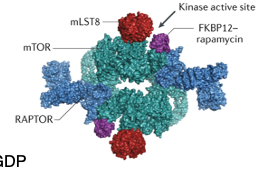


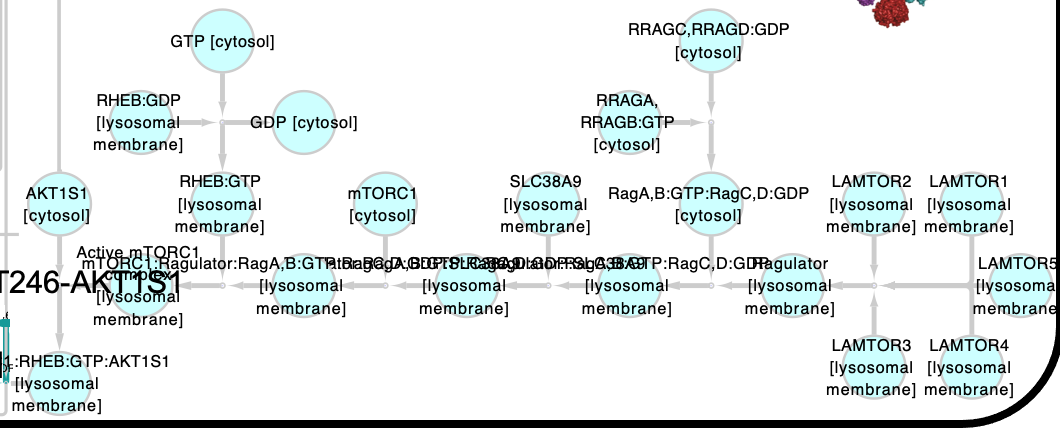
Minimal path

12 connections
13 species
5 pathways

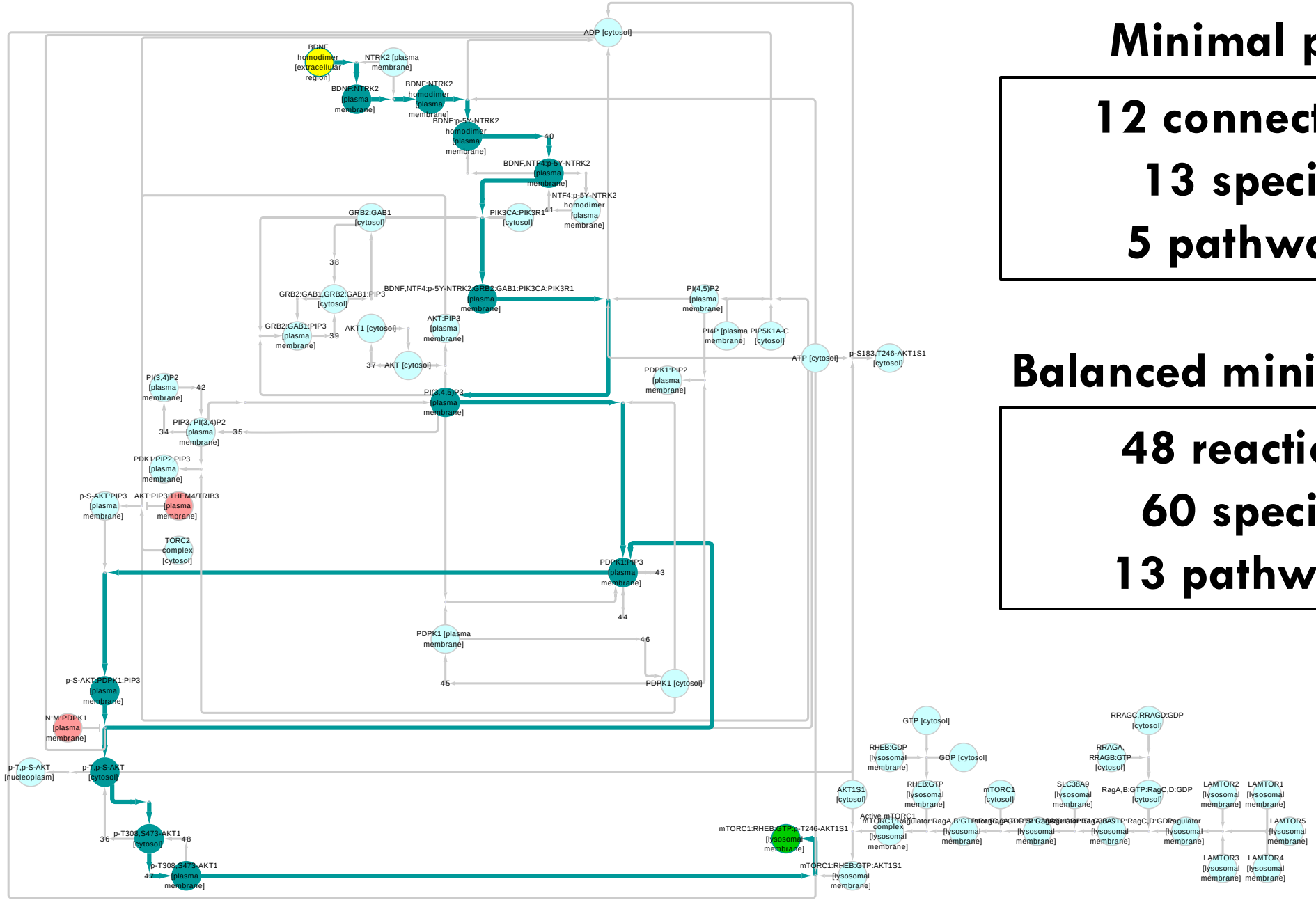


MTOR signaling





Studying BDNF connection to mTOR



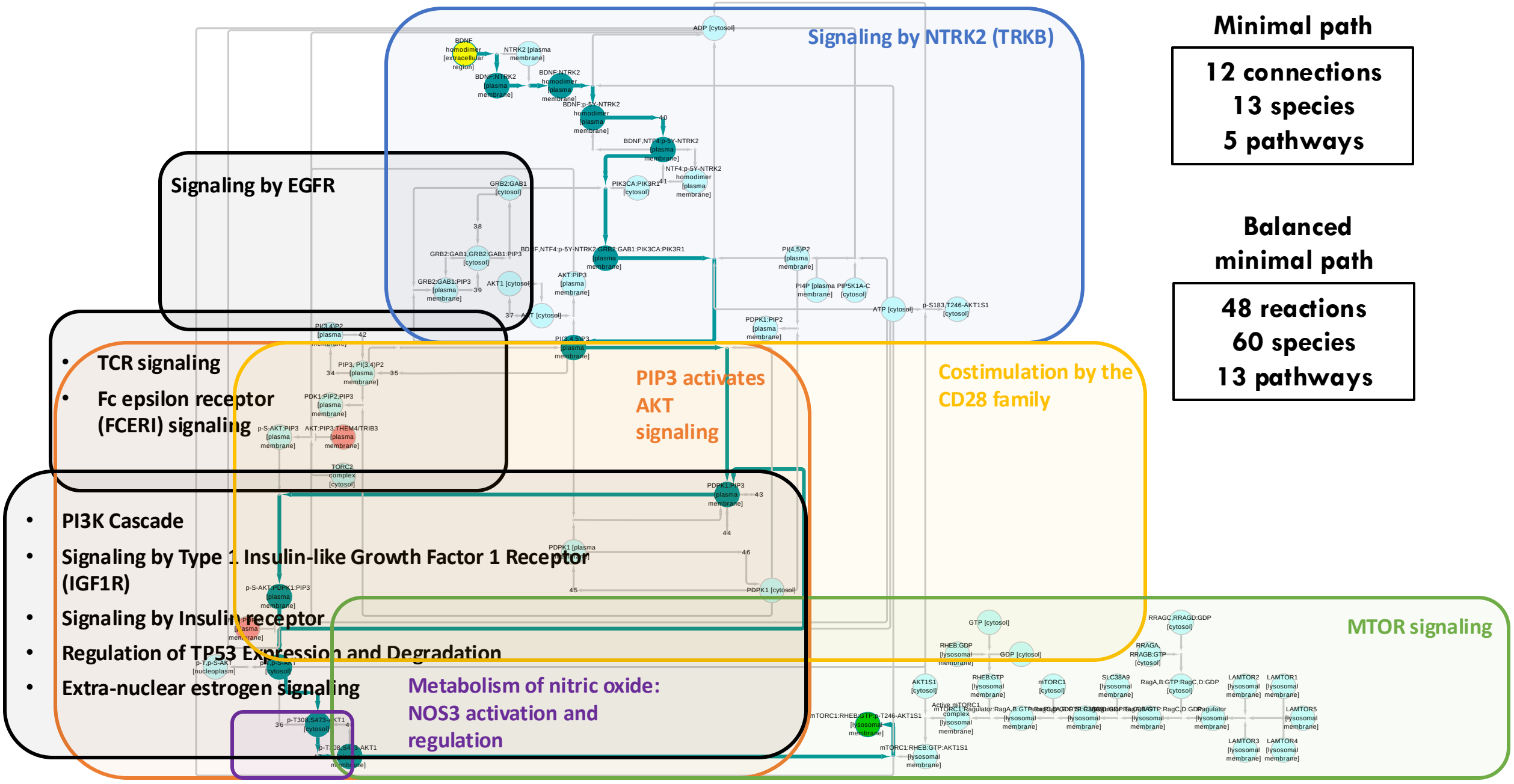
Minimal path

12 connections
13 species
5 pathways

Balanced minimal path

48 reactions
60 species
13 pathways

Studying BDNF connection to mTOR



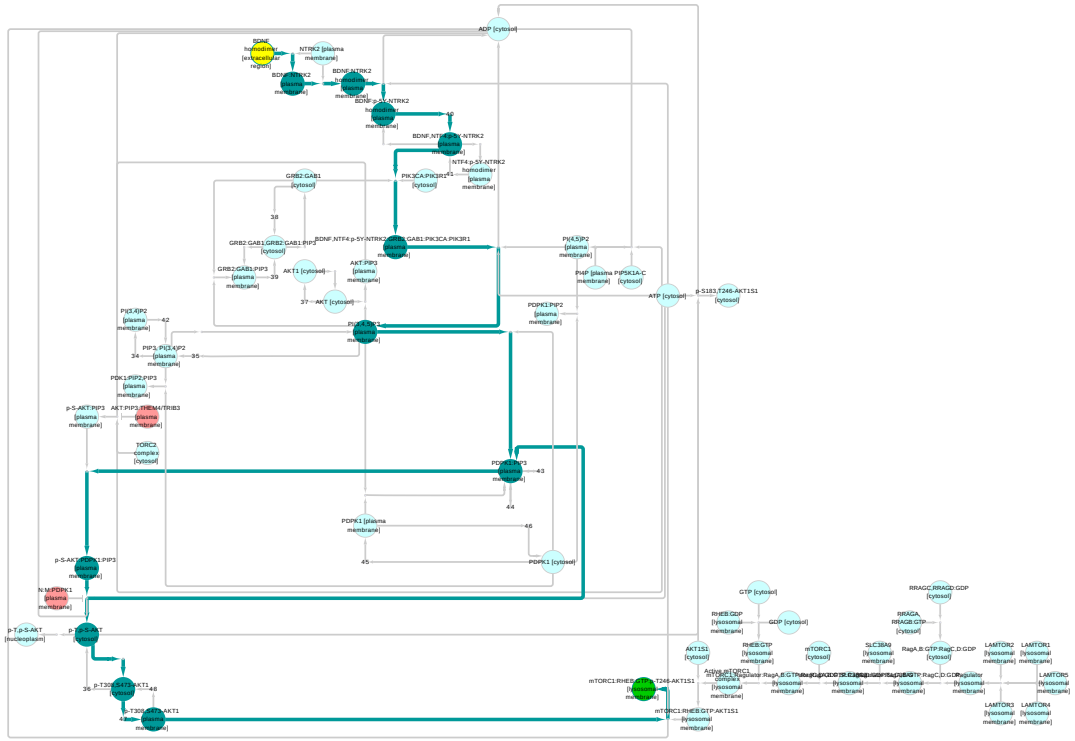
Minimal path

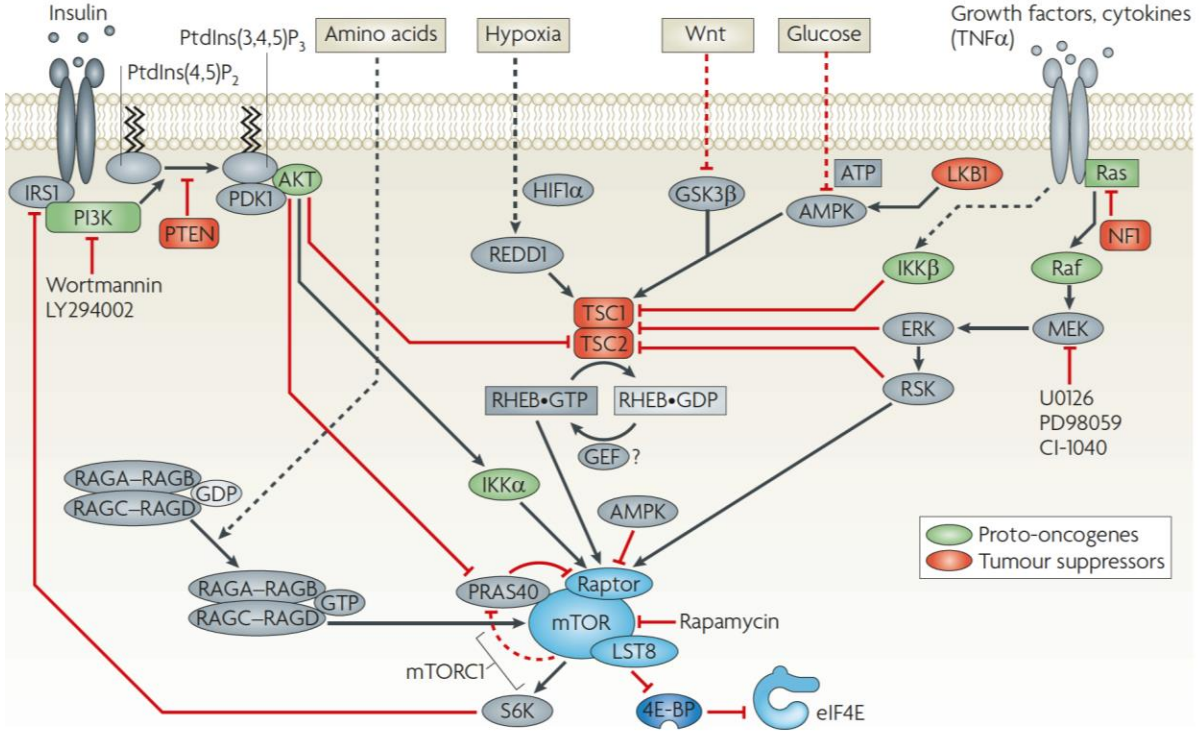
12 connections
13 species
5 pathways

Balanced minimal path

48 reactions
60 species
13 pathways

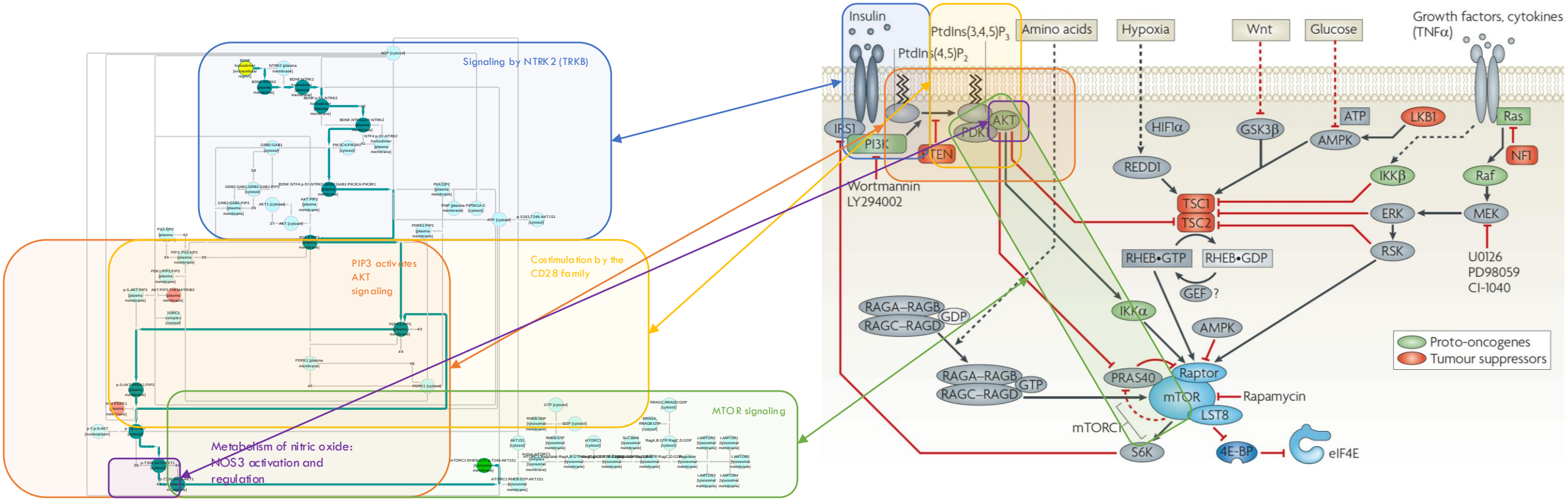
Studying BDNF connection to mTOR





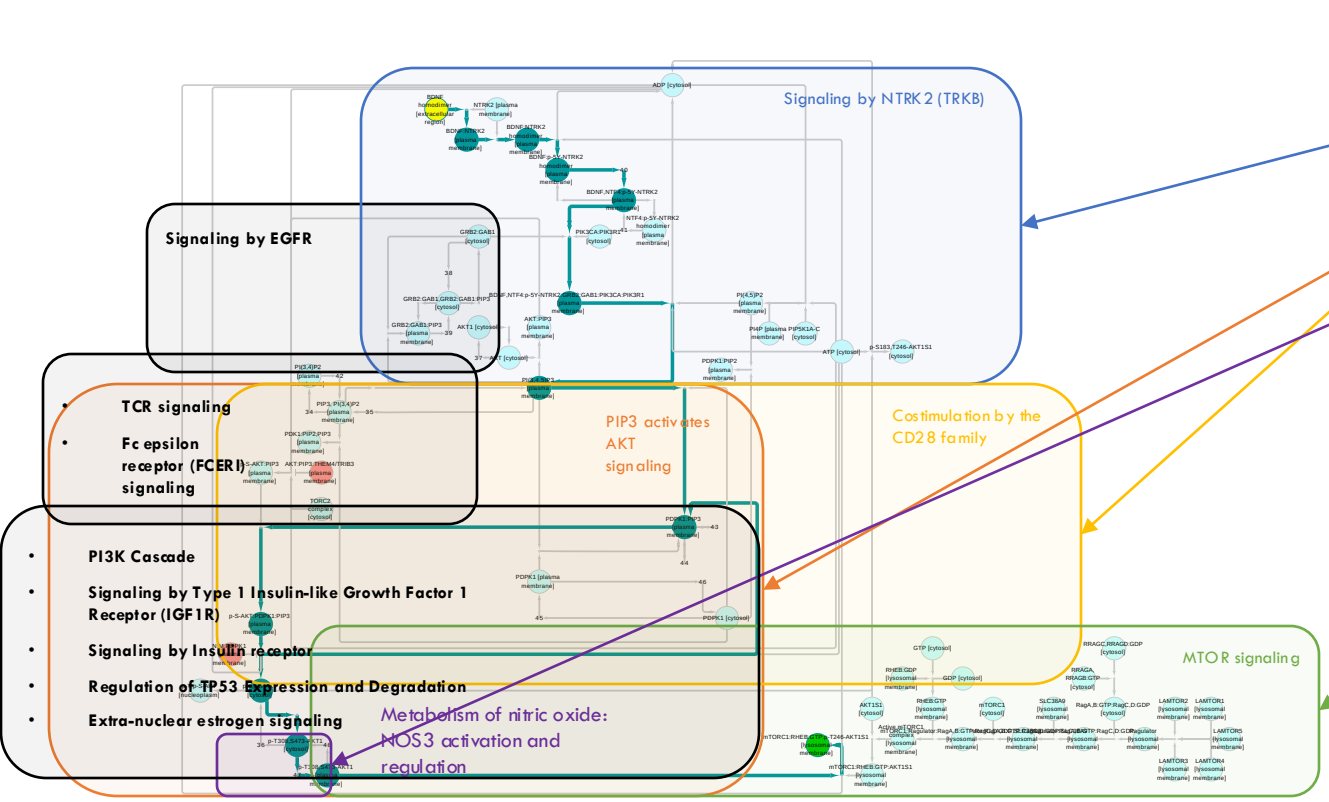
Ma, Xiaoju Max, and John Blenis. "Molecular Mechanisms of MTOR-Mediated Translational Control." *Nature Reviews Molecular Cell Biology*, 2009

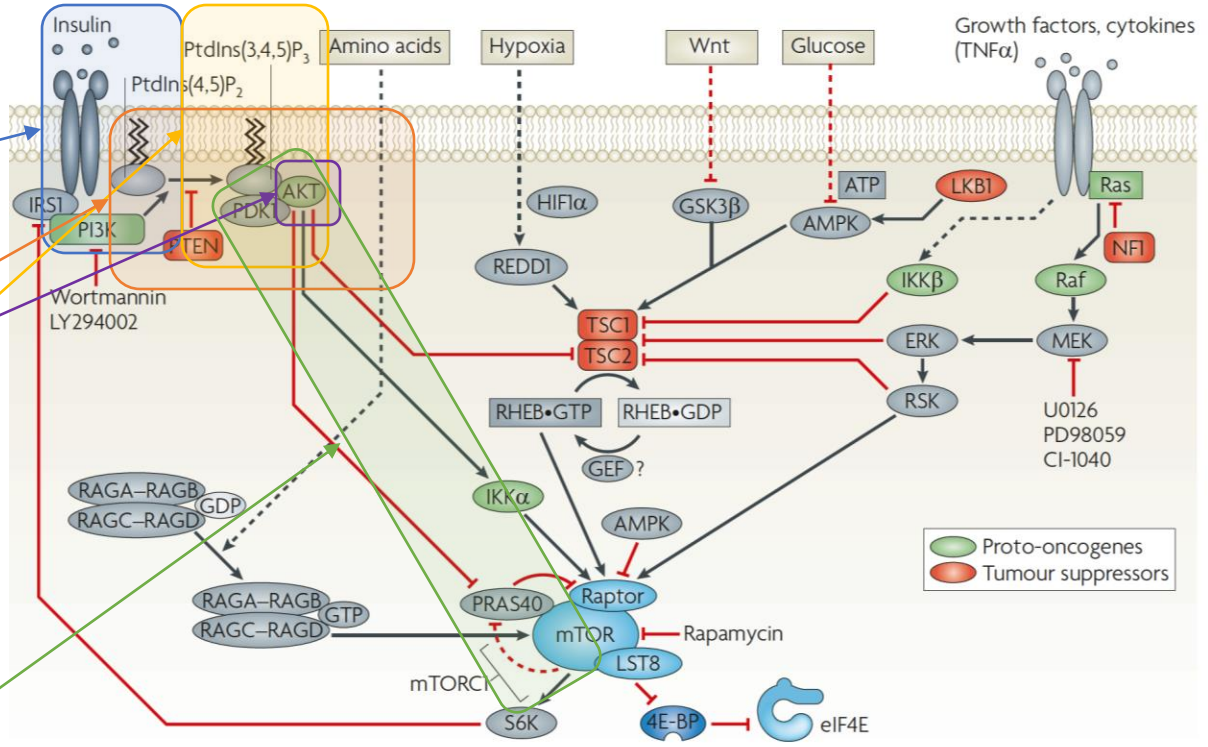
Studying BDNF connection to mTOR



Ma, Xiaoju Max, and John Blenis. "Molecular Mechanisms of MTOR-Mediated Translational Control." *Nature Reviews Molecular Cell Biology*, 2009

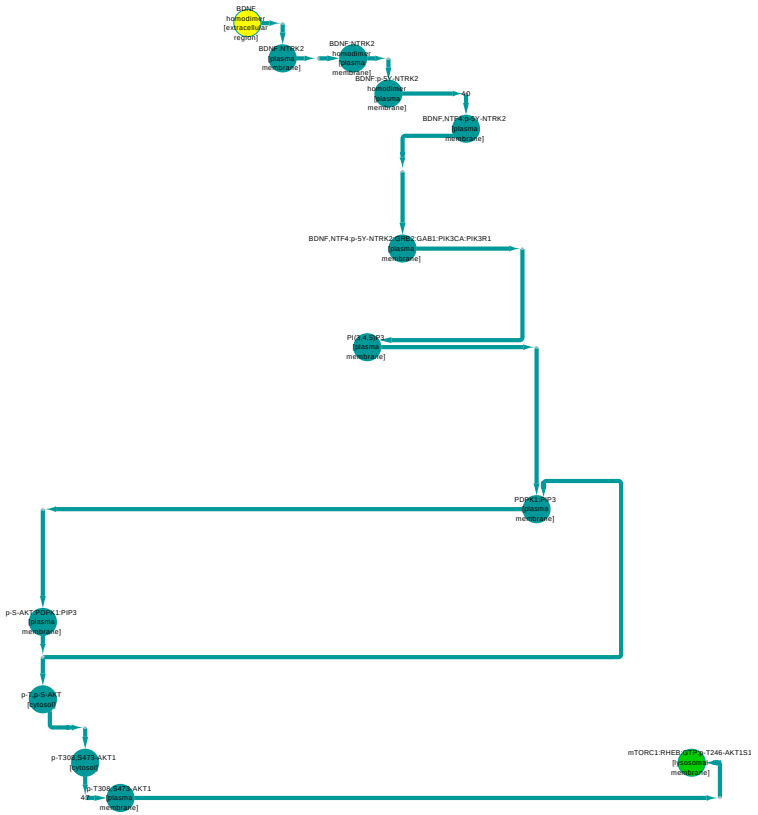
Studying BDNF connection to mTOR





Ma, Xiaoju Max, and John Blenis. "Molecular Mechanisms of MTOR-Mediated Translational Control."
Nature Reviews Molecular Cell Biology, 2009

Alternative BDNF connections to mTOR



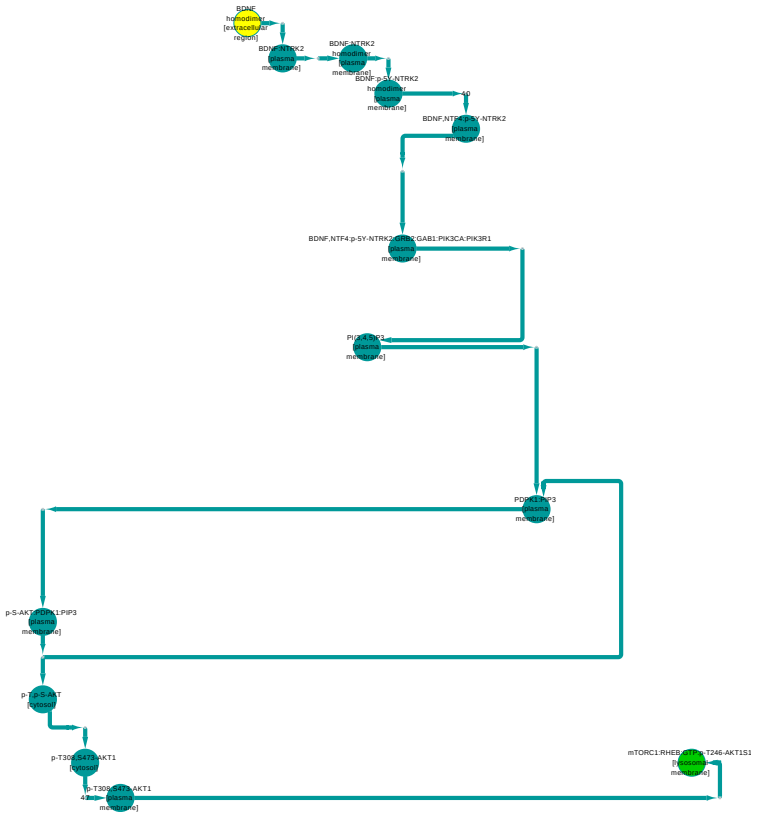
Minimal path

12 connections
13 species
5 pathways

Alternative BDNF connections to mTOR

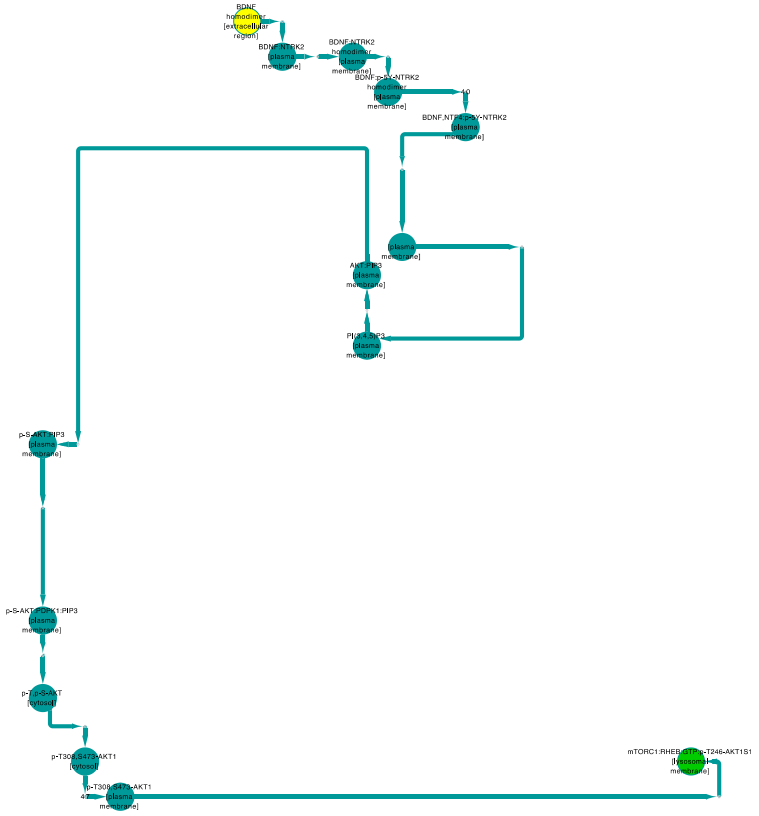
Minimal path

12 connections
13 species
5 pathways



Minimal path+1

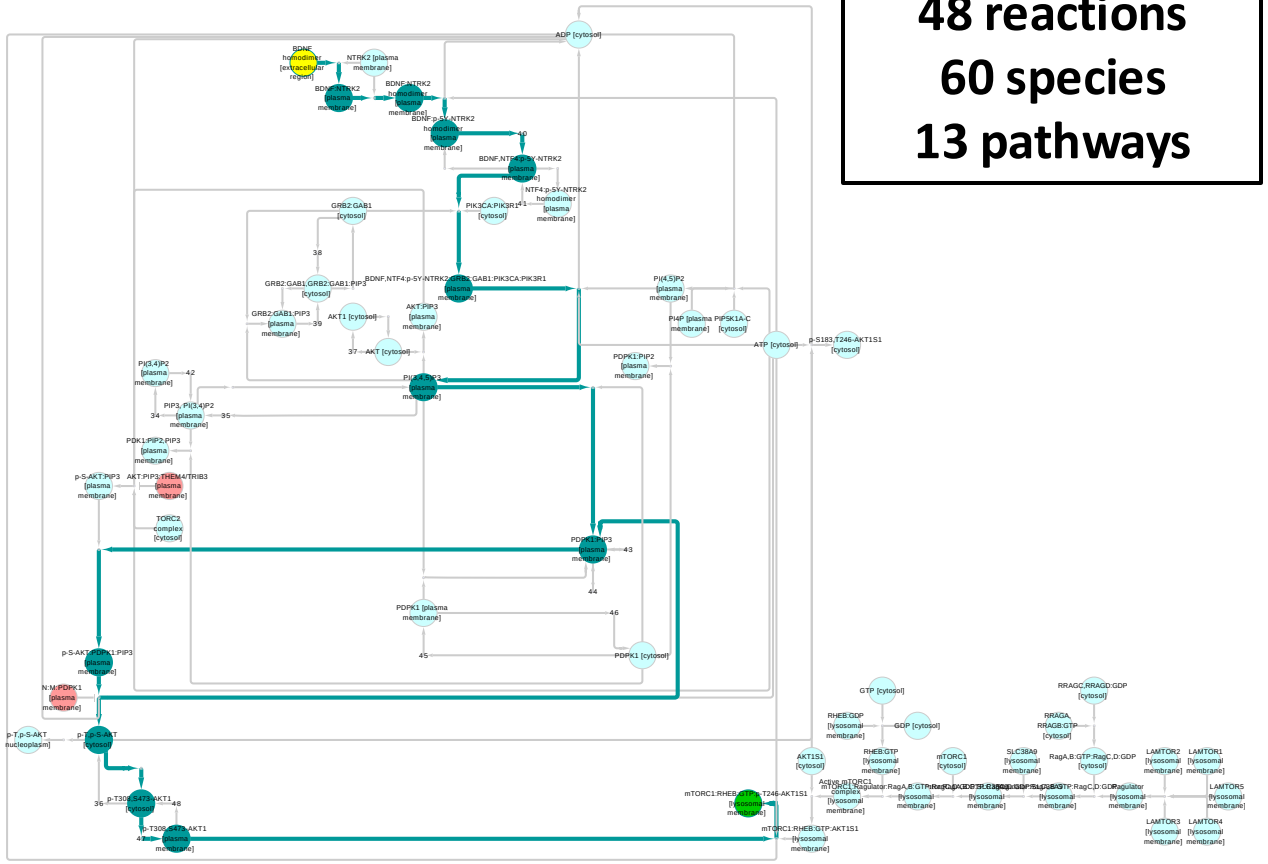
13 connections
14 species
5 pathways



Alternative BDNF connections to mTOR

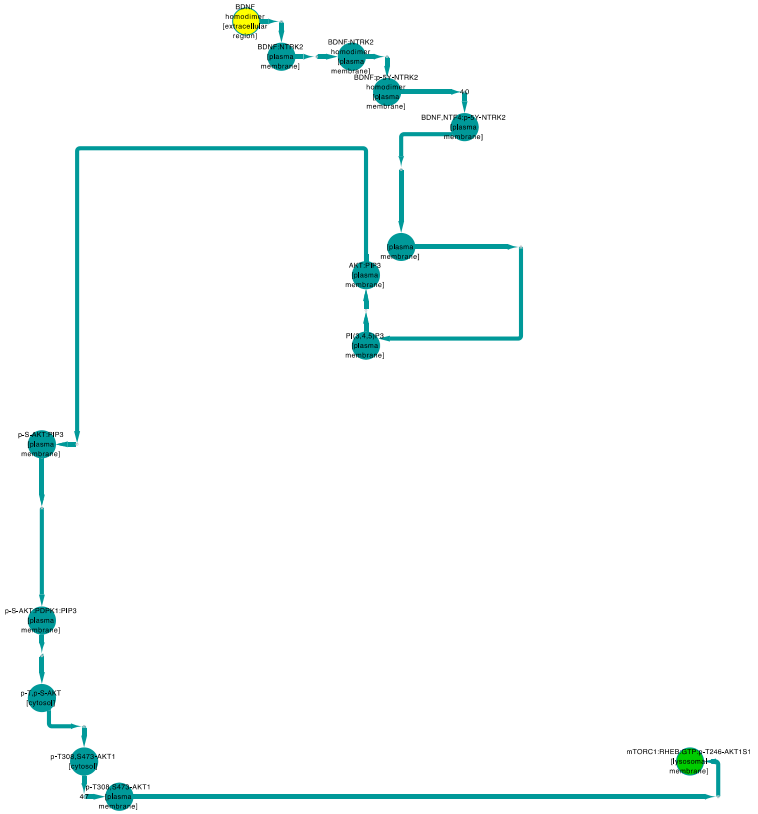
Minimal path

48 reactions
60 species
13 pathways



Minimal path+1

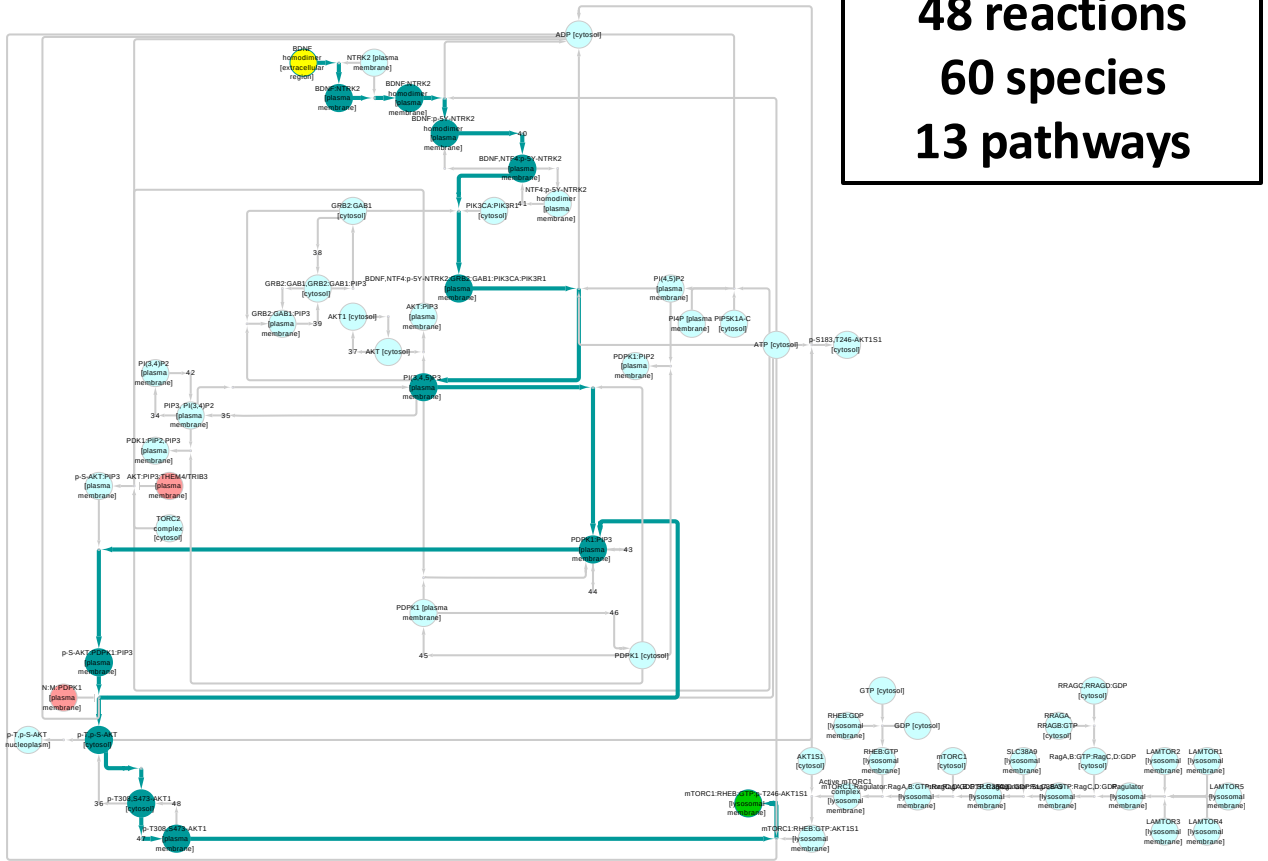
13 connections
14 species
5 pathways



Alternative BDNF connections to mTOR

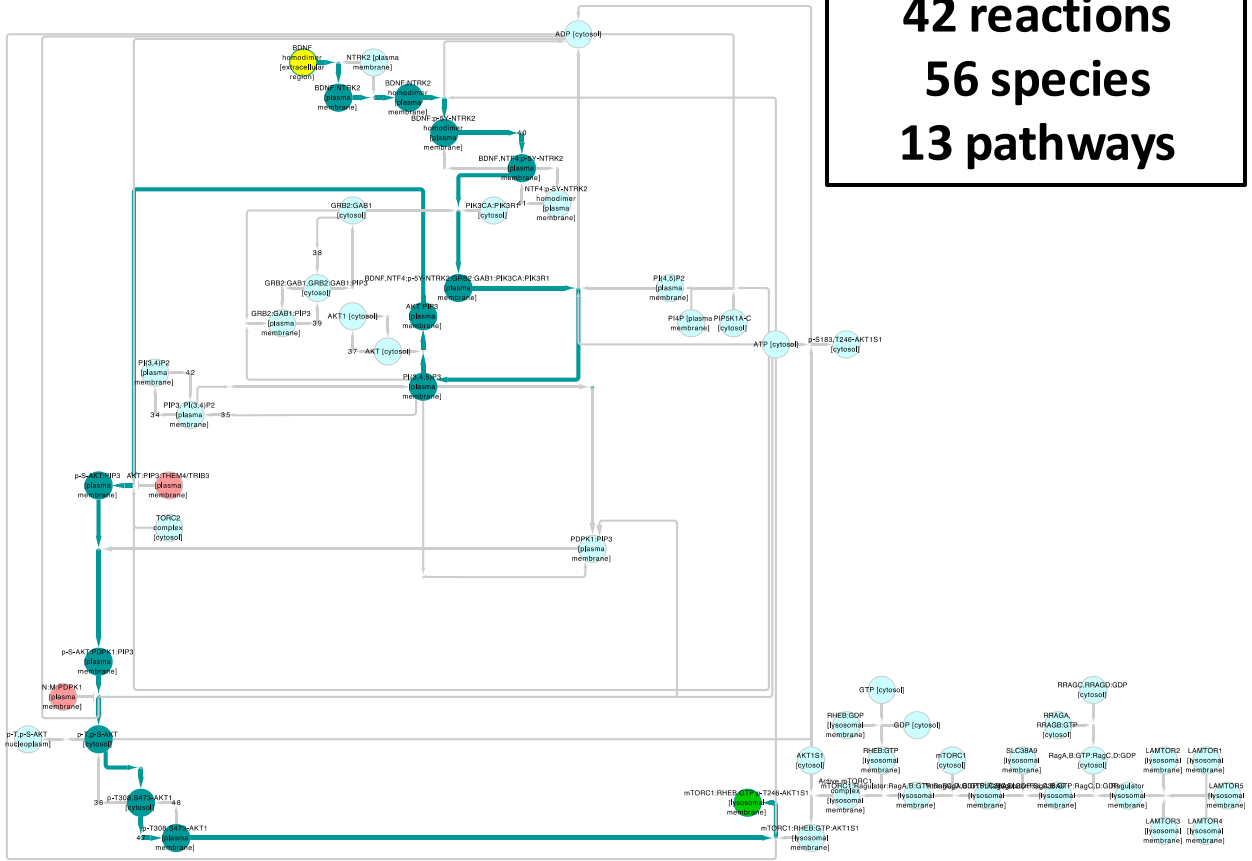
Minimal path

48 reactions
60 species
13 pathways



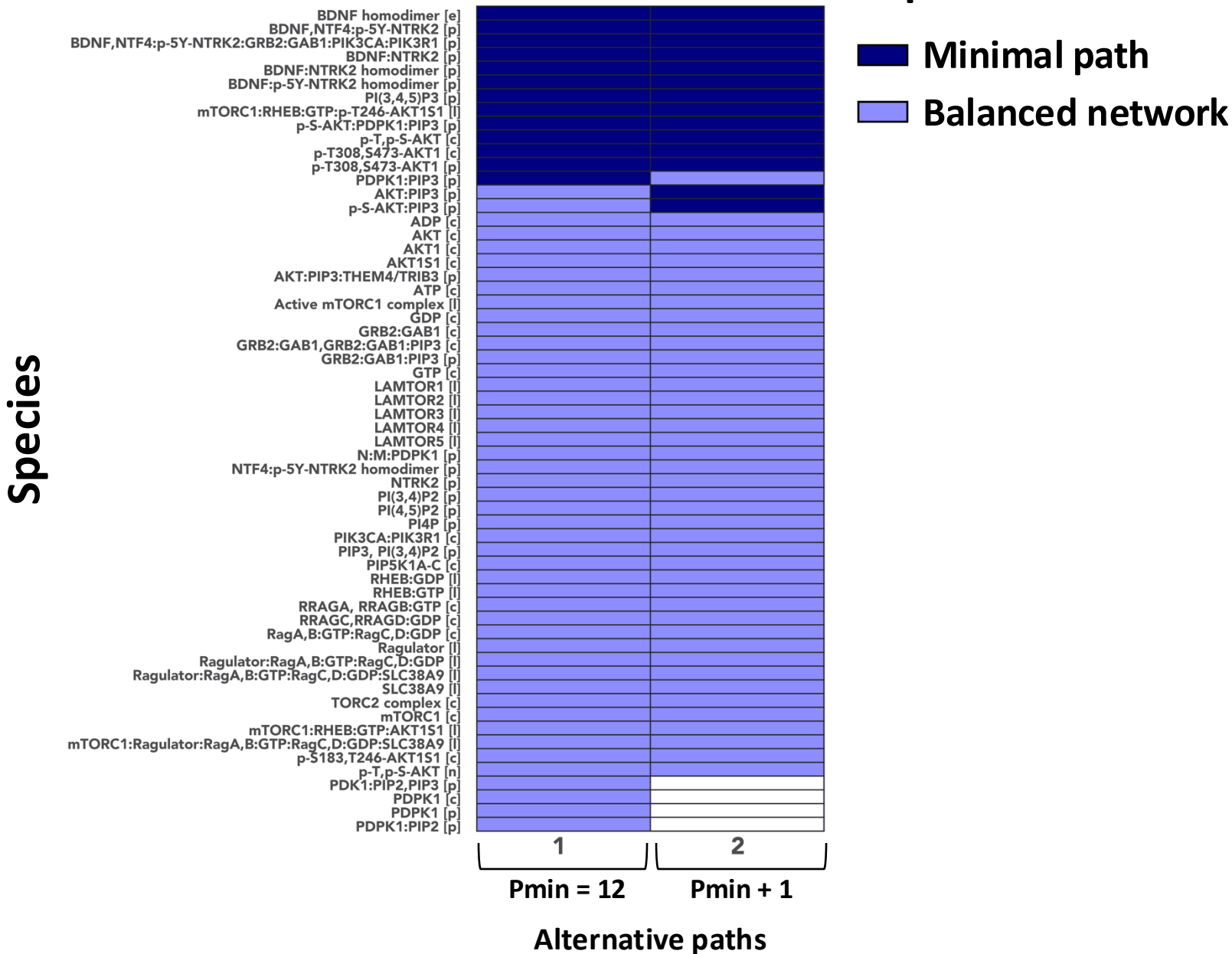
Minimal path+1

42 reactions
56 species
13 pathways



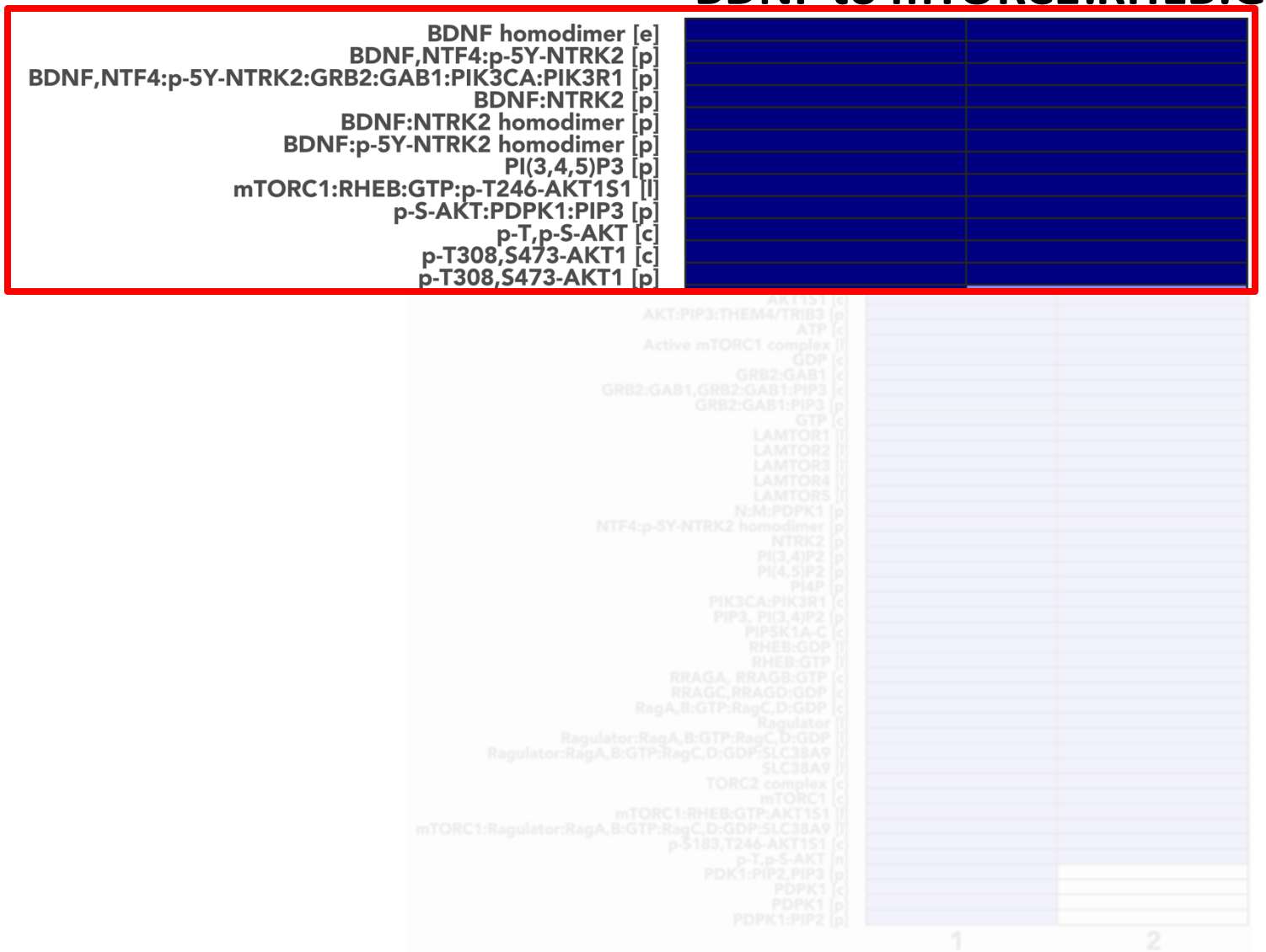
Alternative BDNF connections to mTOR

BDNF to mTORC1:RHEB:GTP:p-T246-AKT1S1



Alternative BDNF connections to mTOR

BDNF to mTORC1:RHEB:GTP:p-T246-AKT1S1

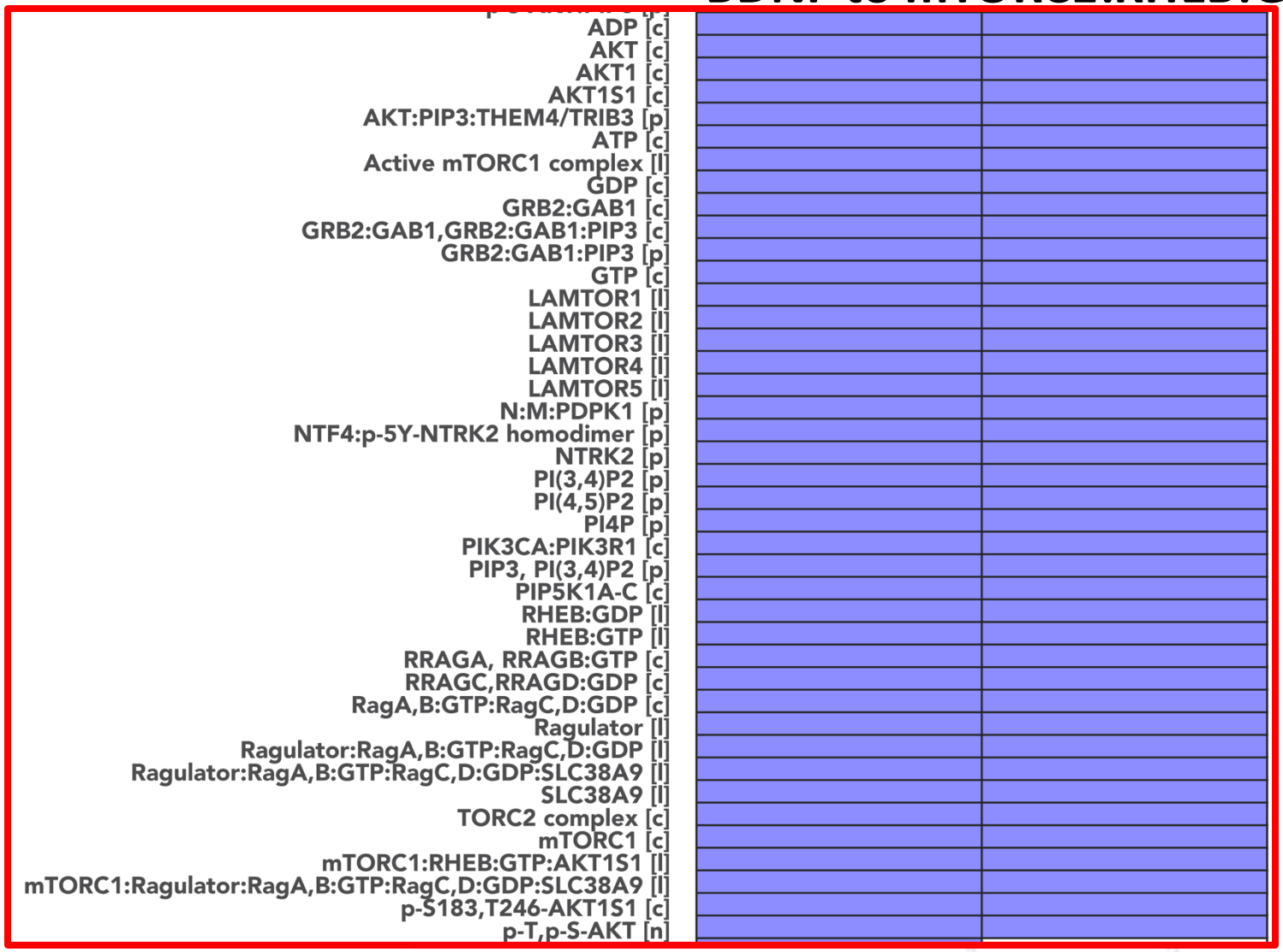


Alternative BDNF connections to mTOR

BDNF to mTORC1:RHEB:GTP:p-T246-AKT1S1

Alternative BDNF connections to mTOR

BDNF to mTORC1:RHEB:GTP:p-T246-AKT1S1



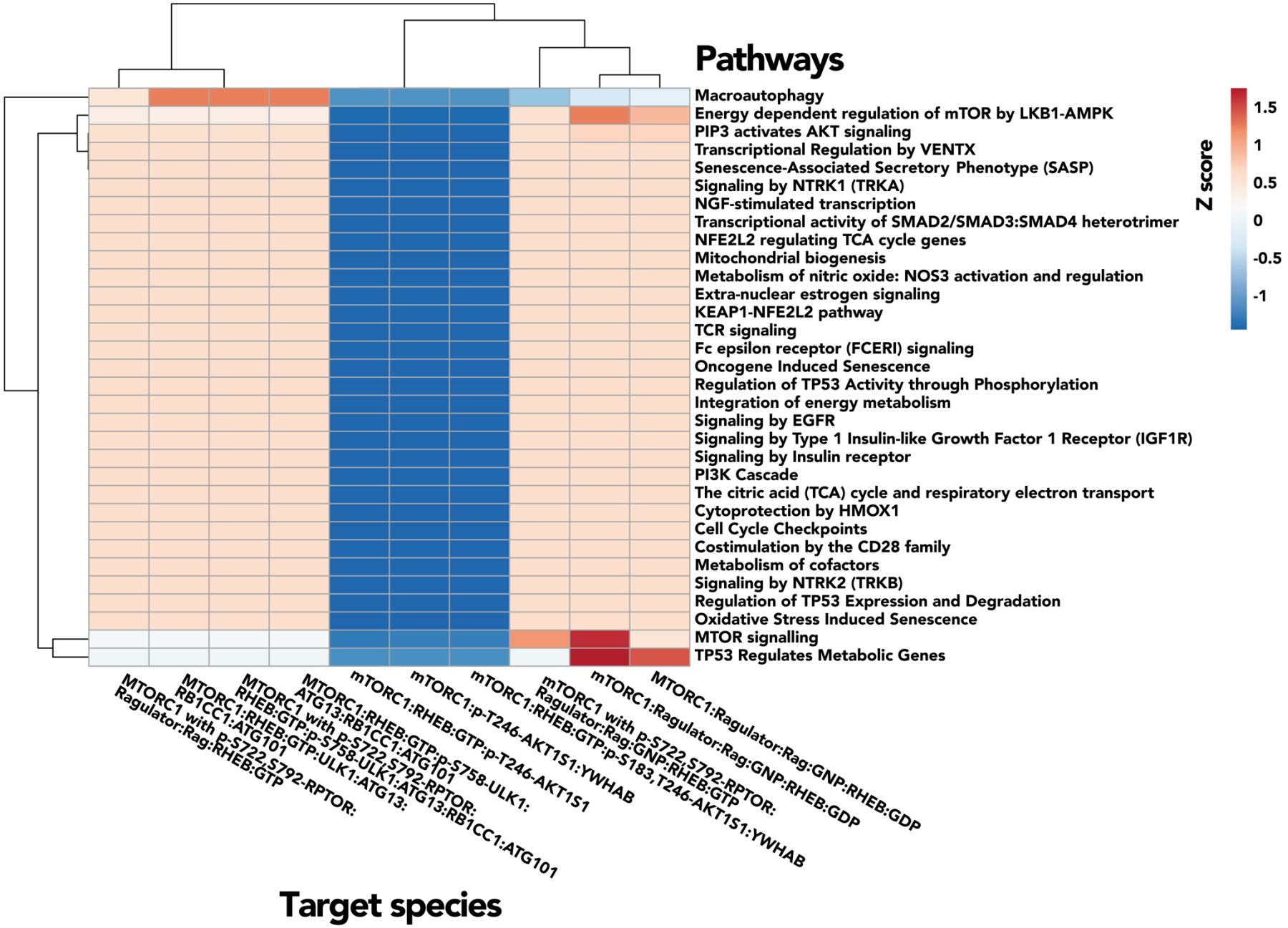
Minimal path

Balanced network

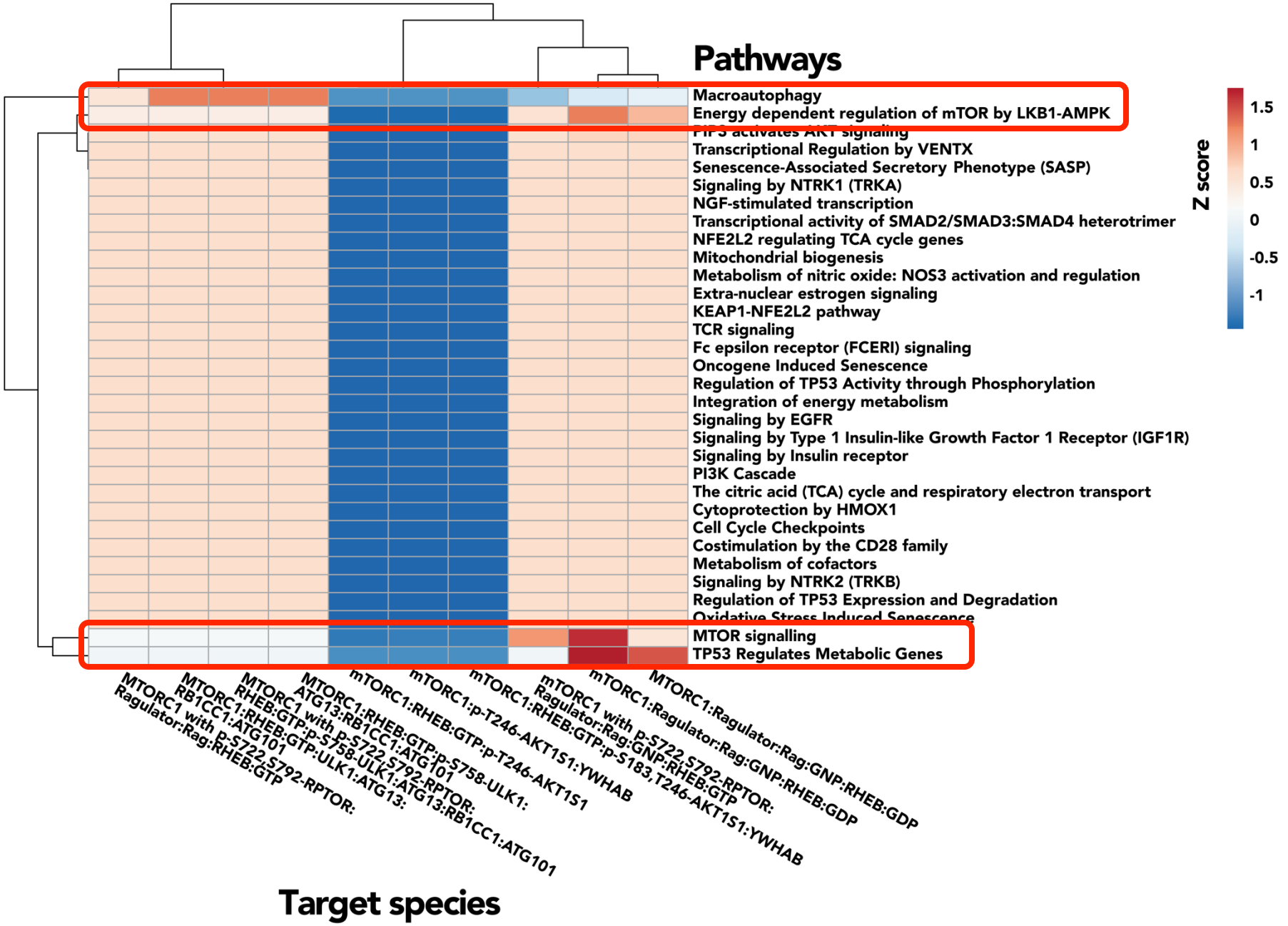
Alternative BDNF connections to mTOR

BDNF to mTORC1:RHEB:GTP:p-T246-AKT1S1

Studying BDNF connection to mTOR

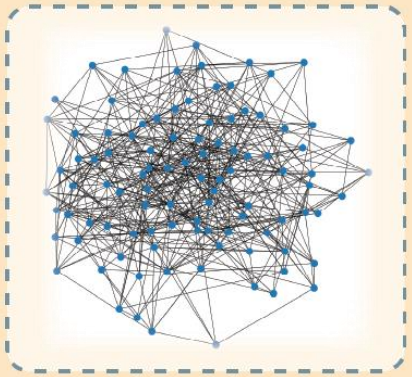


Studying BDNF connection to mTOR



Study deregulation in signaling pathways

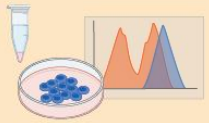
SIGMA Method

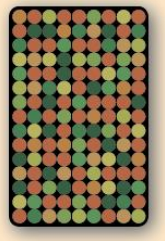


reactome

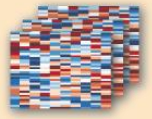
Signaling network

omics data

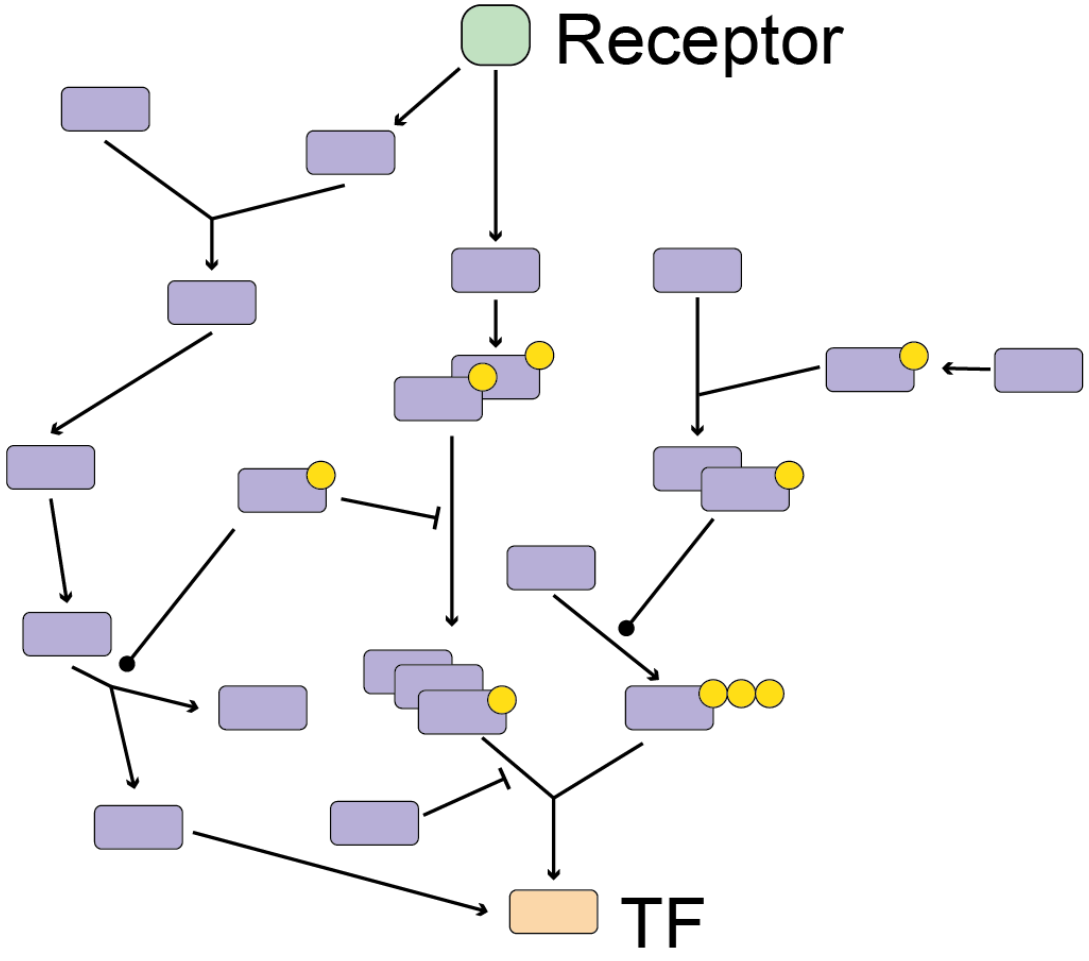




phosphoproteomics

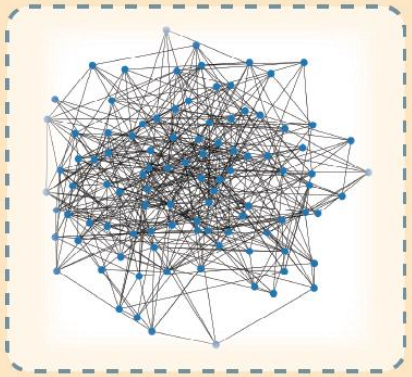


(sc)RNA-seq data



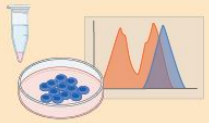
Study deregulation in signaling pathways

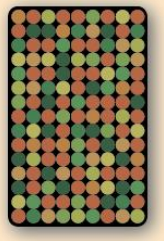
SIGMA Method



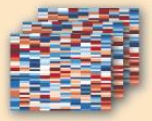
Signaling network

omics data



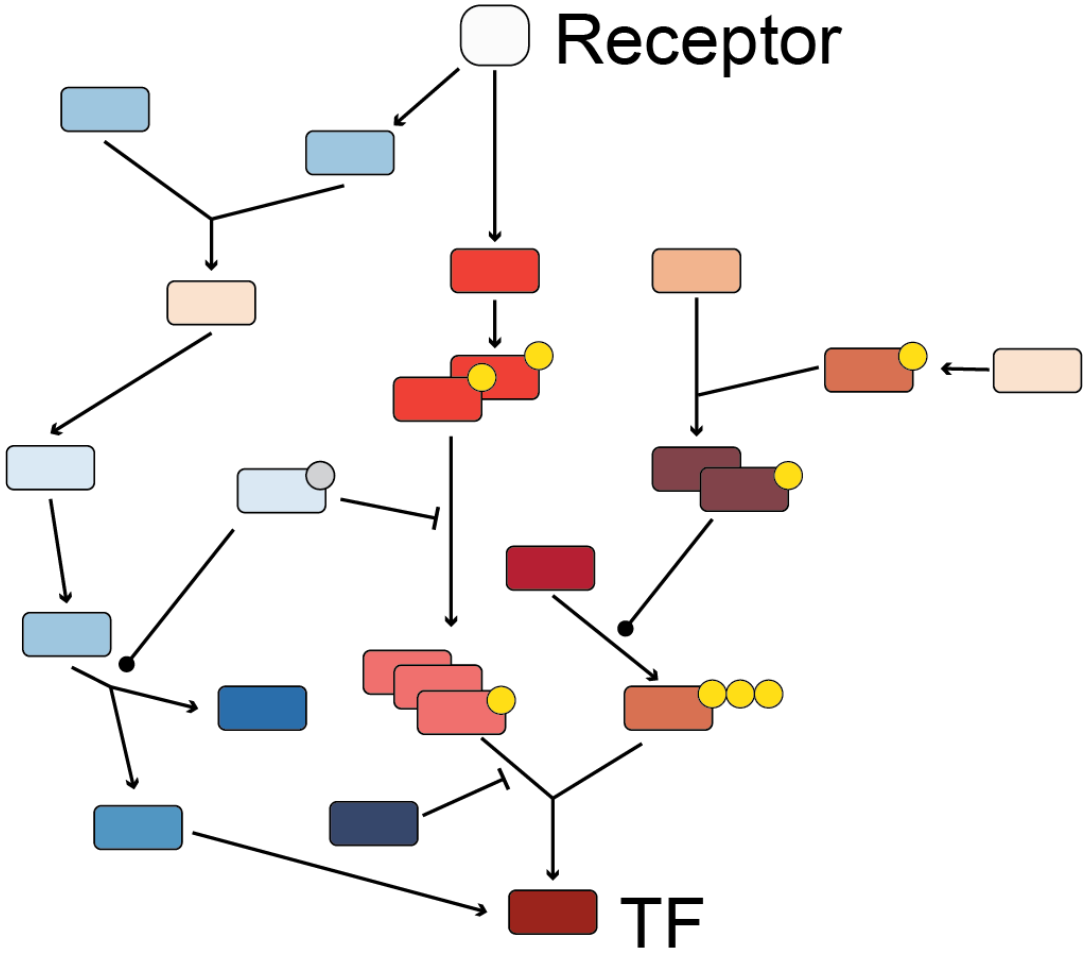


phosphoproteomics



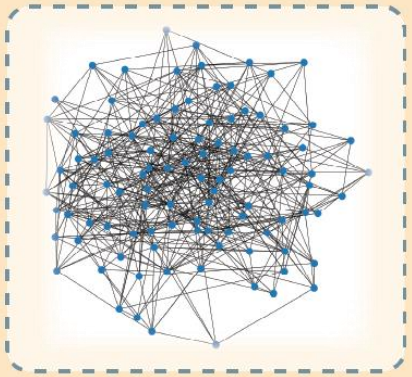
(sc)RNA-seq data

"*network* enrichment" analysis
(vs. pathway enrichment analysis)



Study deregulation in signaling pathways

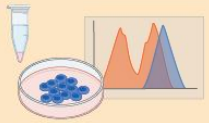
SIGMA Method

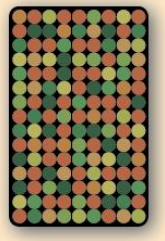


reactome

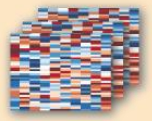
Signaling network

omics data

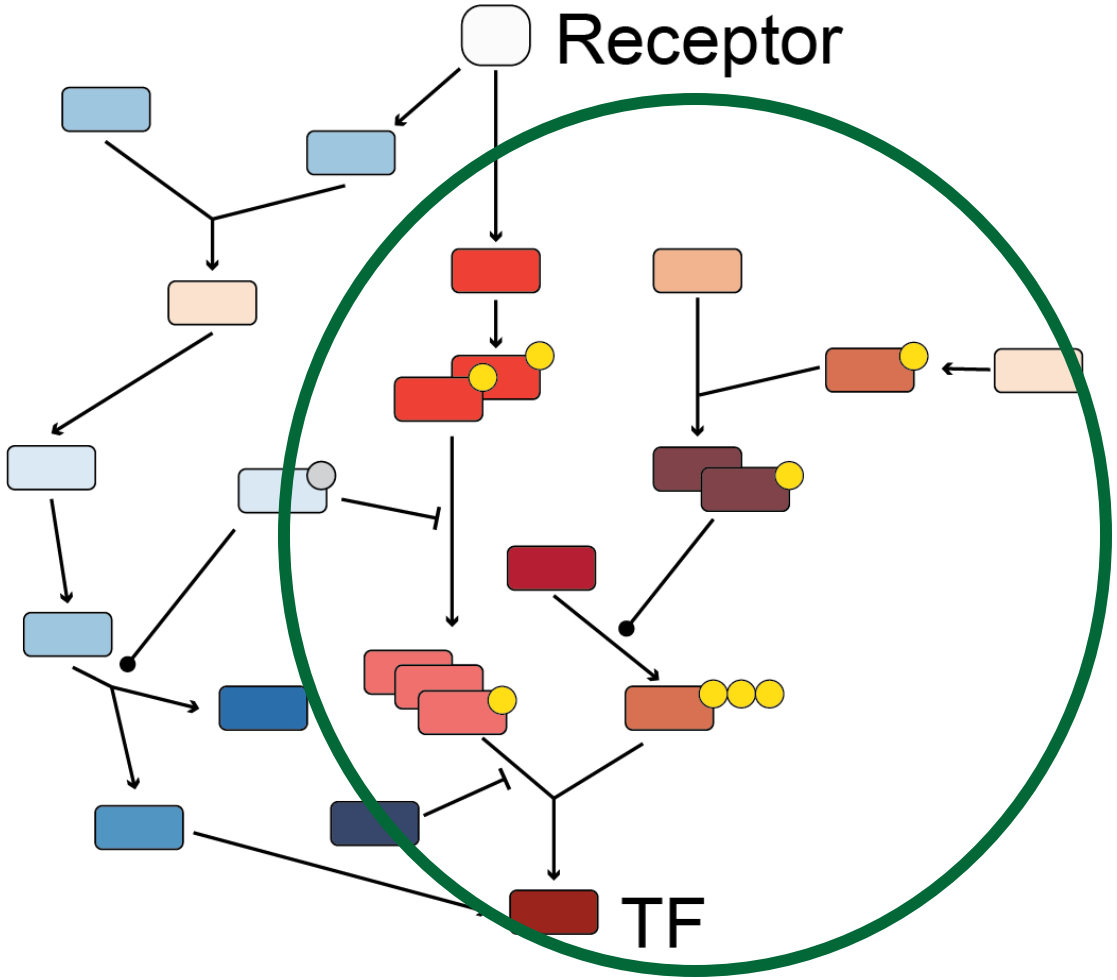




phosphoproteomics

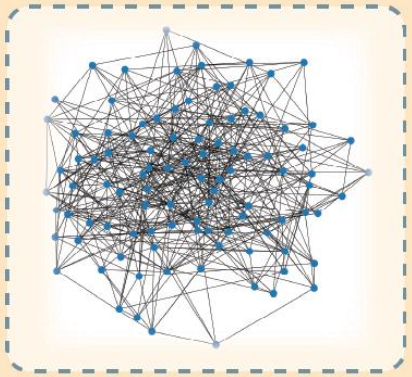


(sc)RNA-seq data



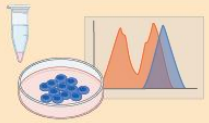
Study deregulation in signaling pathways

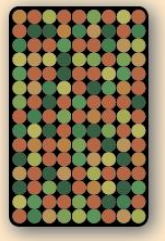
SIGMA Method



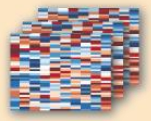
Signaling network

omics data



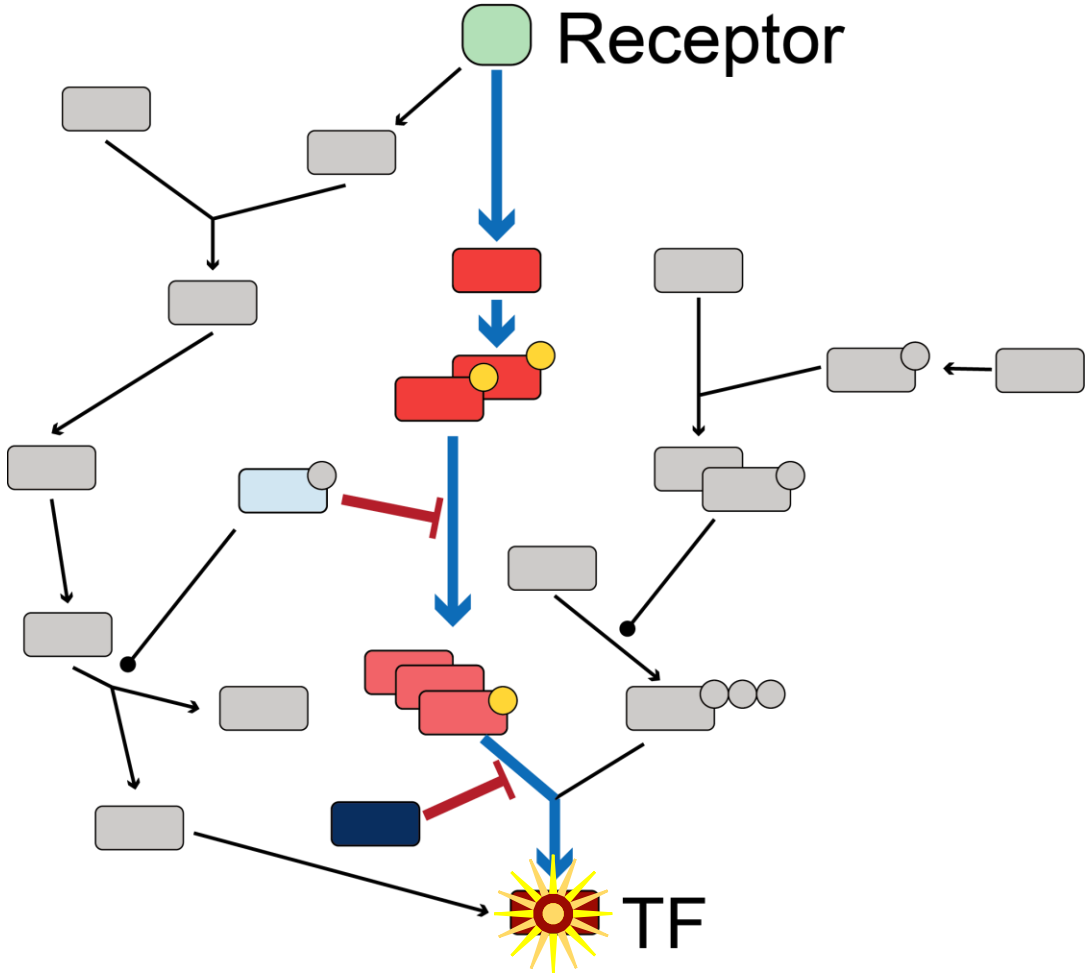


phosphoproteomics



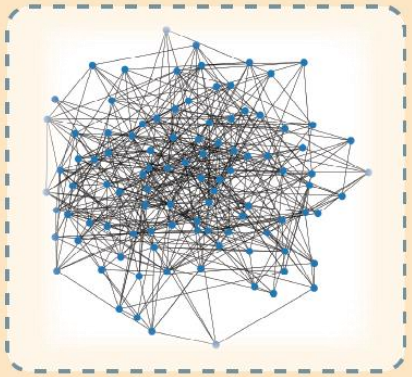
(sc)RNA-seq data

canonical pathway



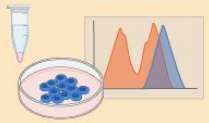
Study deregulation in signaling pathways

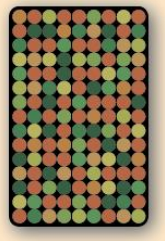
SIGMA Method



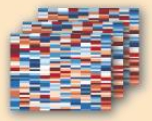
Signaling network

omics data



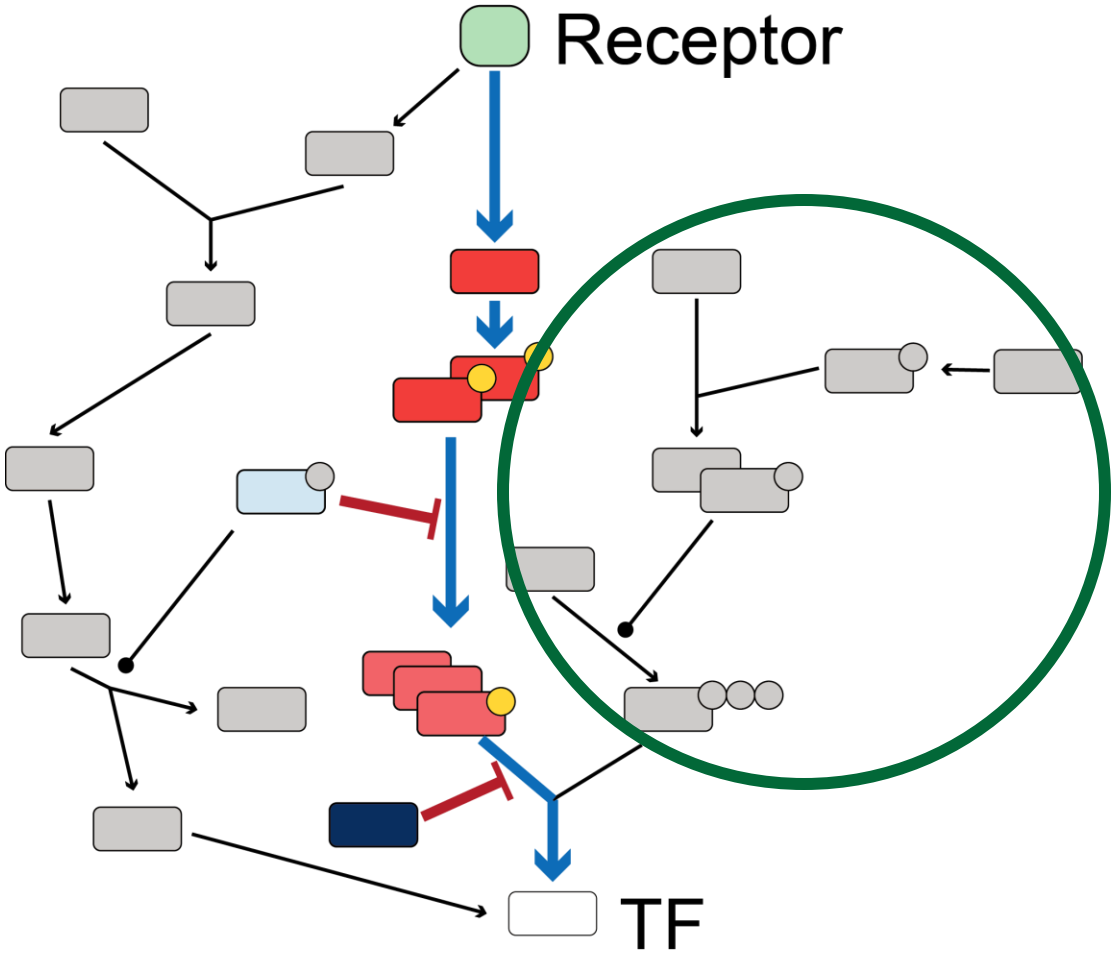


phosphoproteomics



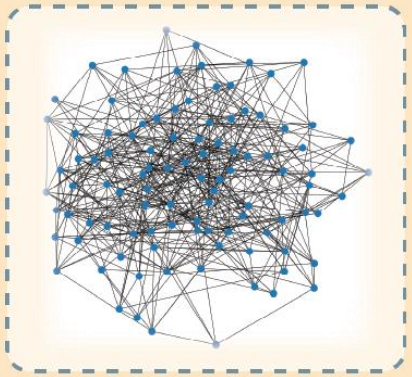
(sc)RNA-seq data

peripheral pathways



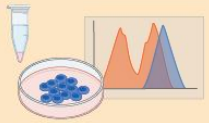
Study deregulation in signaling pathways

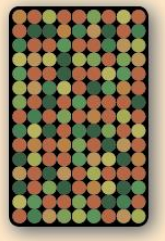
SIGMA Method



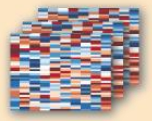
Signaling network

omics data



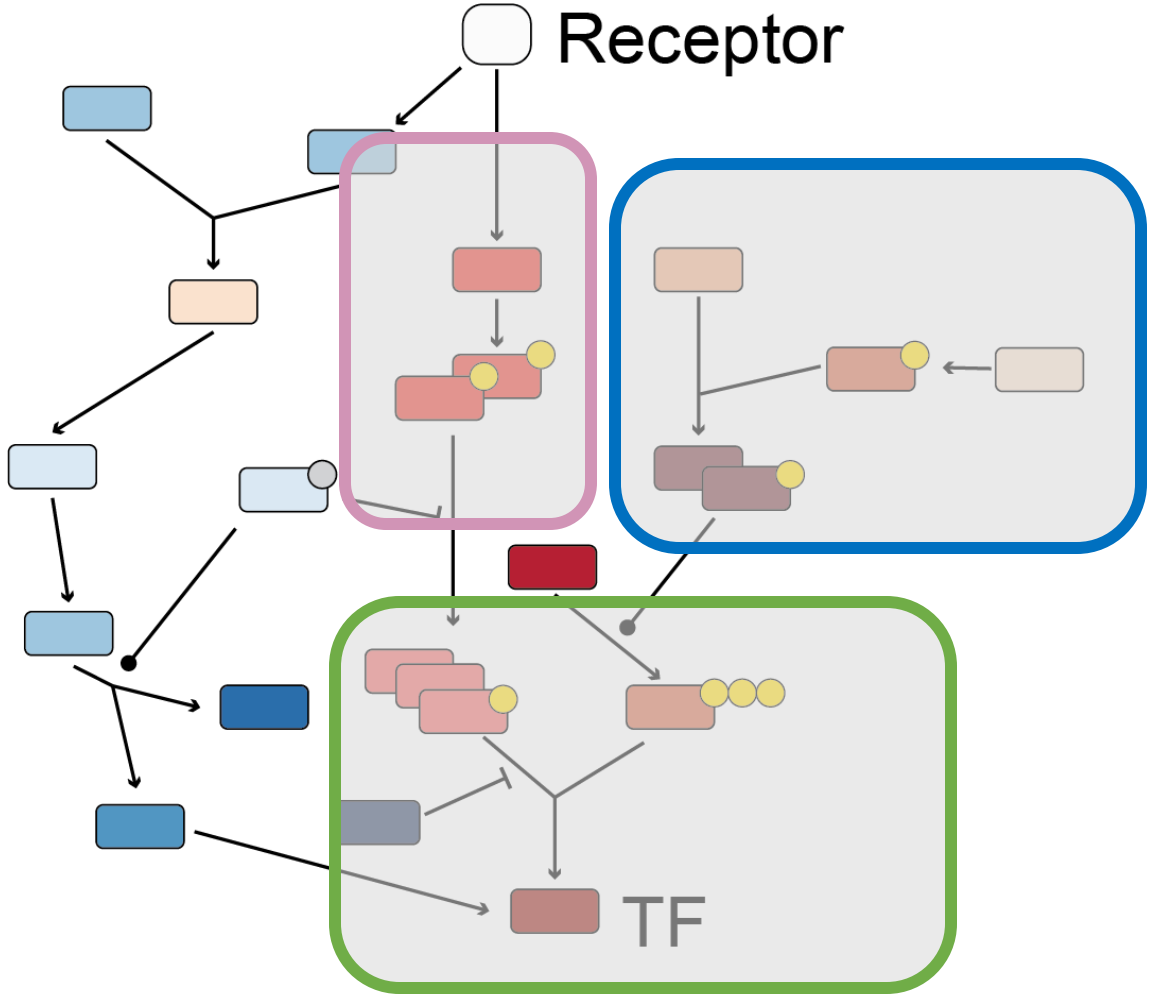


phosphoproteomics



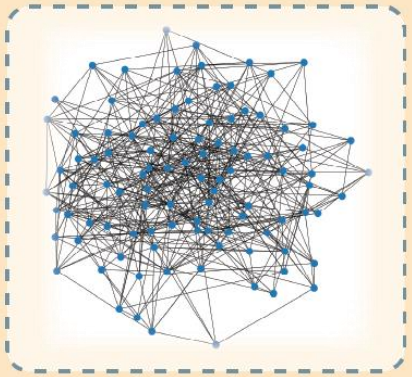
(sc)RNA-seq data

pathway cross-talk



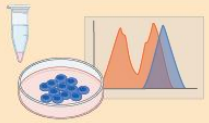
Study deregulation in signaling pathways

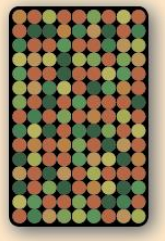
SIGMA Method



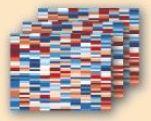
Signaling network

omics data



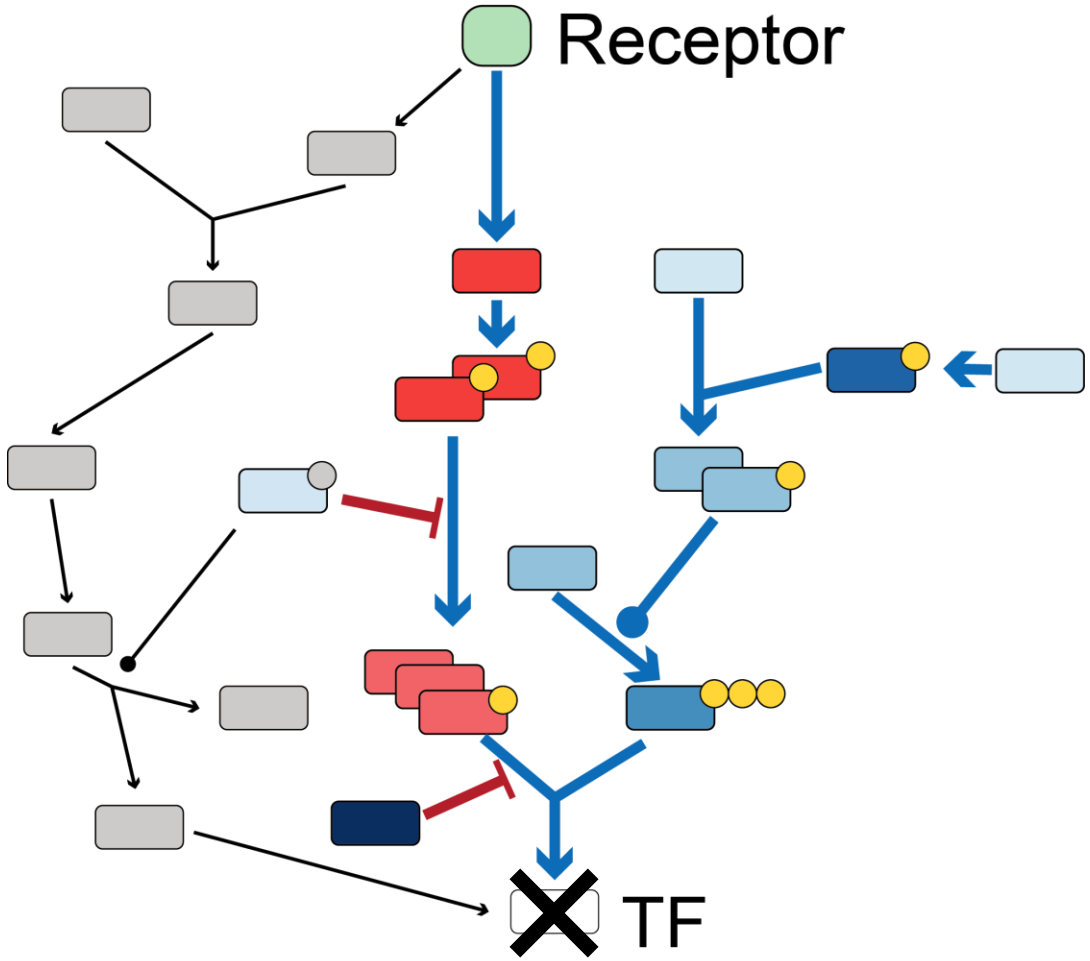


phosphoproteomics



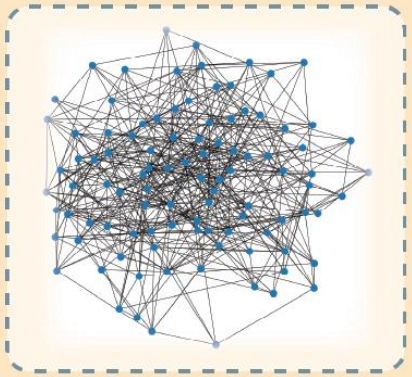
(sc)RNA-seq data

peripheral pathways are critical!



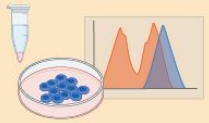
Study deregulation in signaling pathways

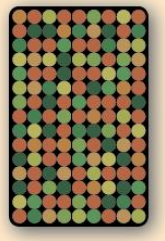
SIGMA Method



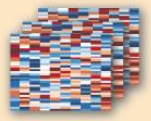
Signaling network

omics data



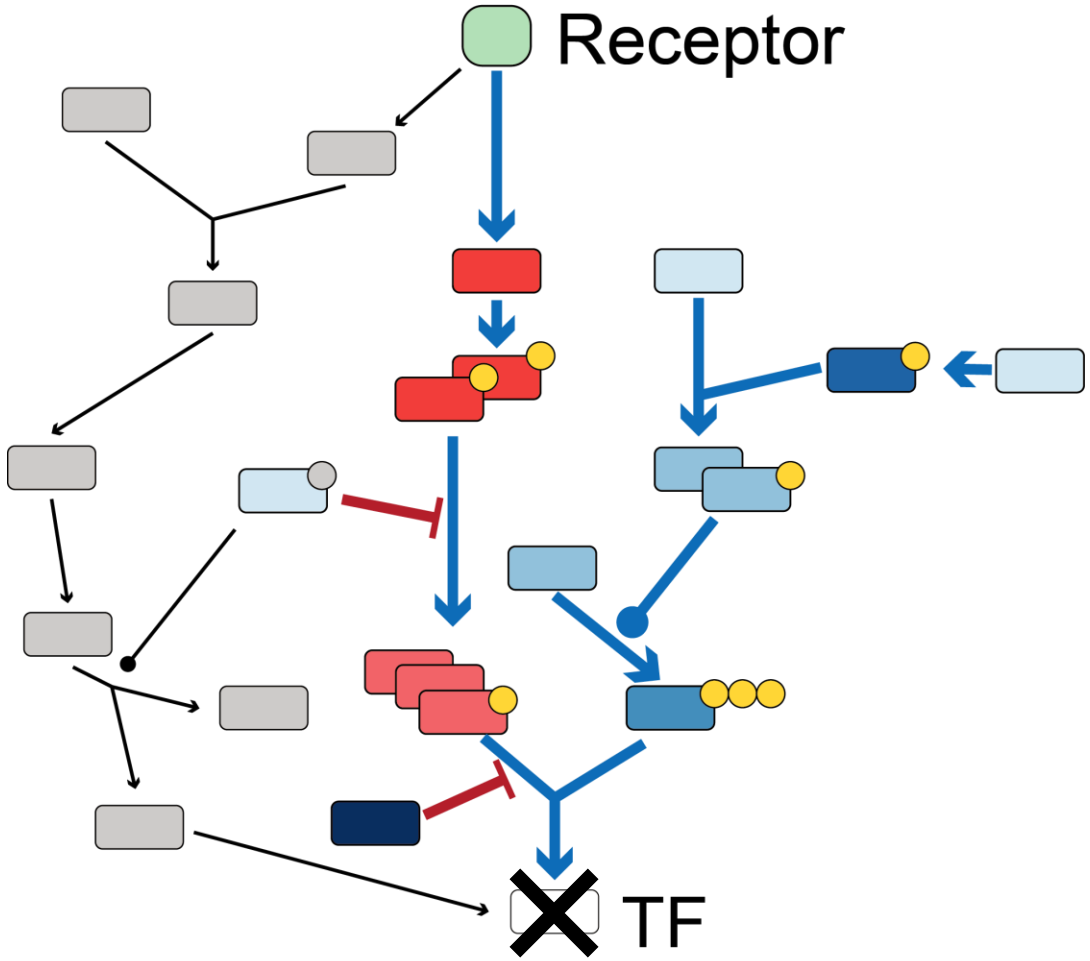


phosphoproteomics

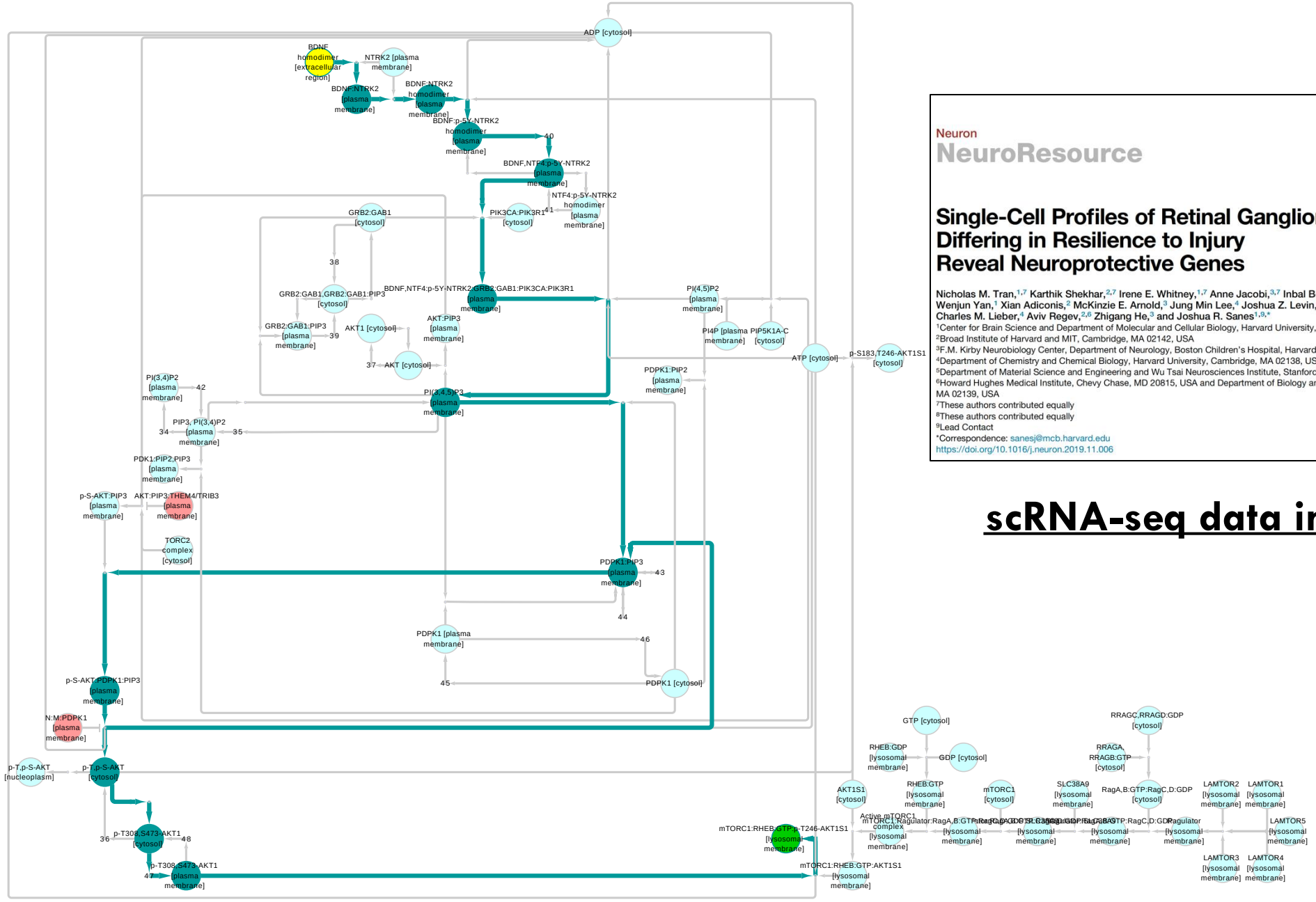


(sc)RNA-seq data

peripheral pathways are critical!



Studying BDNF connection to mTOR



Neuron
NeuroResource
CellPress

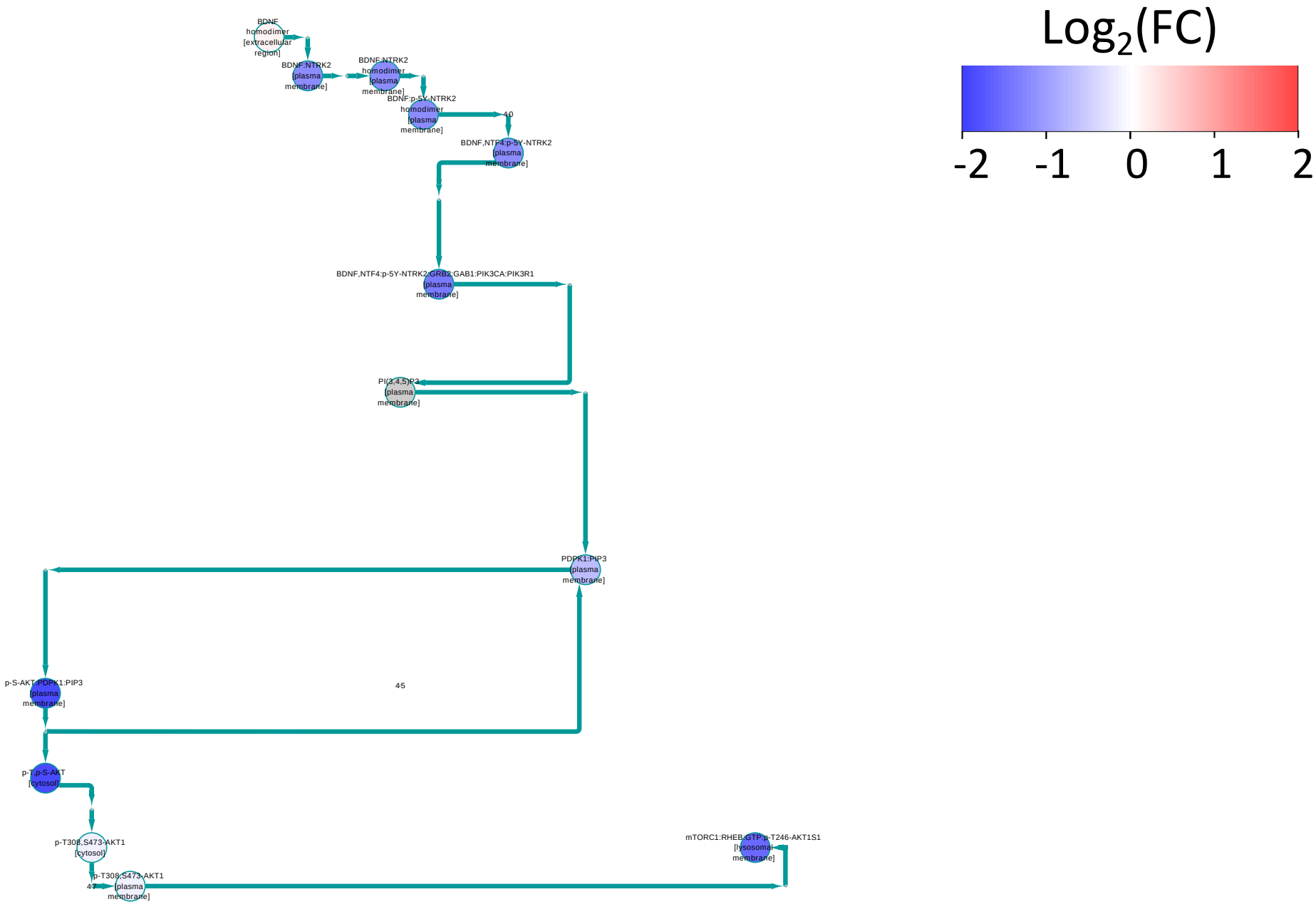
Single-Cell Profiles of Retinal Ganglion Cells Differing in Resilience to Injury Reveal Neuroprotective Genes

Nicholas M. Tran,[1,7] Karthik Shekhar,[2,7] Irene E. Whitney,[1,7] Anne Jacobi,[3,7] Inbal Benhar,[2,8] Guosong Hong,[4,5,8] Wenjun Yan,[1] Xian Adiconis,[2] McKinzie E. Arnold,[3] Jung Min Lee,[4] Joshua Z. Levin,[2] Dingchang Lin,[4] Chen Wang,[3] Charles M. Lieber,[4] Aviv Regev,[2,6] Zhigang He,[3] and Joshua R. Sanes[1,9,*]

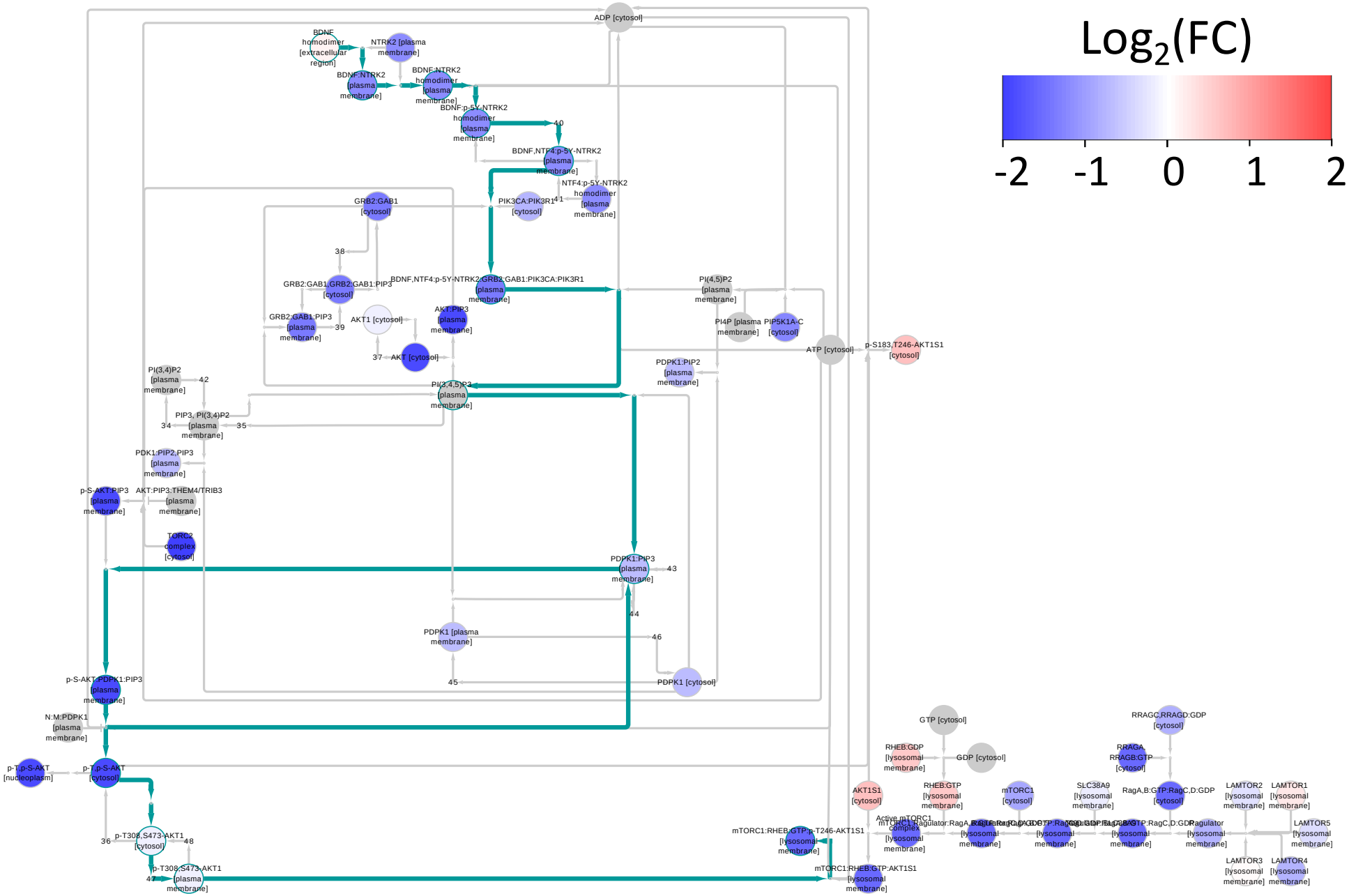
[1]Center for Brain Science and Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA, USA
[2]Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA
[3]F.M. Kirby Neurobiology Center, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA
[4]Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, USA
[5]Department of Material Science and Engineering and Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA 94305, USA
[6]Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA and Department of Biology and Koch Institute, MIT, Cambridge, MA 02139, USA
[7]These authors contributed equally
[8]These authors contributed equally
[9]Lead Contact
*Correspondence: sanesj@mcb.harvard.edu
https://doi.org/10.1016/j.neuron.2019.11.006

scRNA-seq data integration

Studying BDNF connection to mTOR



Studying BDNF connection to mTOR



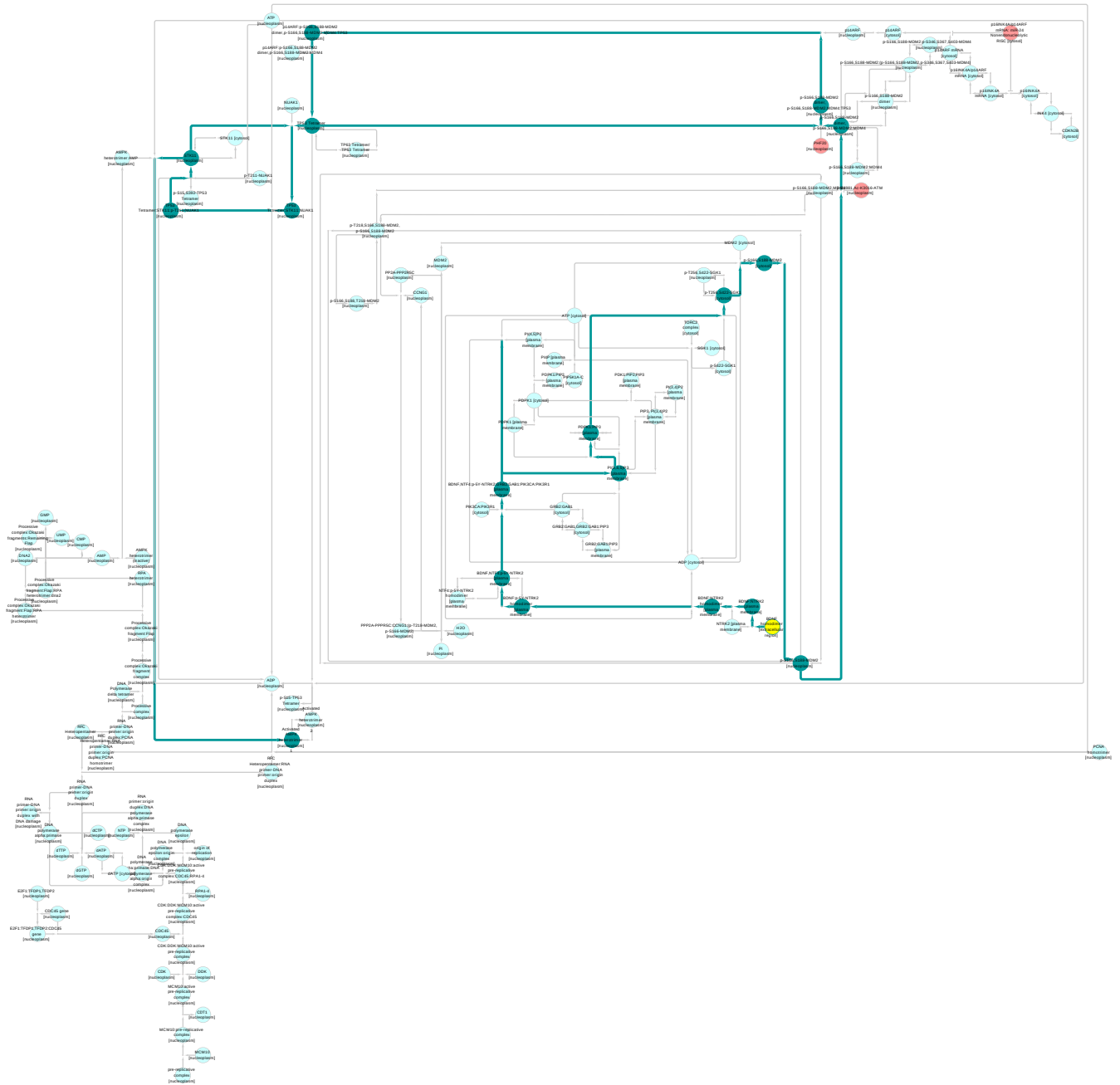
Studying BDNF connection to AMPK

Start	Target	Result	Min path
BDNF homodimer [e]	Activated AMPK heterotrimer [n]	YES	18
BDNF homodimer [e]	AMPK heterotrimer (active) [c]	NO	-
BDNF homodimer [e]	AMPK heterotrimer (inactive) [n]	NO	-
BDNF homodimer [e]	AMPK heterotrimer [c]	YES	21
BDNF homodimer [e]	AMPK heterotrimer:AMP [n]	NO	-
BDNF homodimer [e]	AMPK-alpha2:AMPK-beta:AMPK-gamma:AMP [c]	NO	-
BDNF homodimer [e]	p-AMPK heterotrimer [c]	YES	20
BDNF homodimer [e]	p-AMPK heterotrimer:AMP [c]	YES	21
BDNF homodimer [e]	p-AMPK heterotrimer:AMP [n]	YES	22
BDNF homodimer [e]	p-AMPK heterotrimer:AMP:p-S317,467,556,638,T575-ULK1: ATG13:RB1CC1:ATG101 [c]	YES	23
BDNF homodimer [e]	p-AMPK heterotrimer:AMP:p-T180,S317,467,556,638,T575-ULK1: ATG13:RB1CC1:ATG101 [c]	YES	24
BDNF homodimer [e]	p-AMPK heterotrimer:AMP:p-T180,S317,467,556,638,T575-ULK1: ATG13:RB1CC1:ATG101 [er]	YES	26
BDNF homodimer [e]	p-AMPK heterotrimer:AMP:p-T180,S317,467,556,638,T575-ULK1: p-ATG13:p-RB1CC1:ATG101 [c]	YES	25
BDNF homodimer [e]	p-AMPK heterotrimer:AMP:ULK1:ATG13:RB1CC1:ATG101 [c]	YES	22
BDNF homodimer [e]	SESN1,2,3:p-AMPK heterotrimer:AMP [c]	YES	17

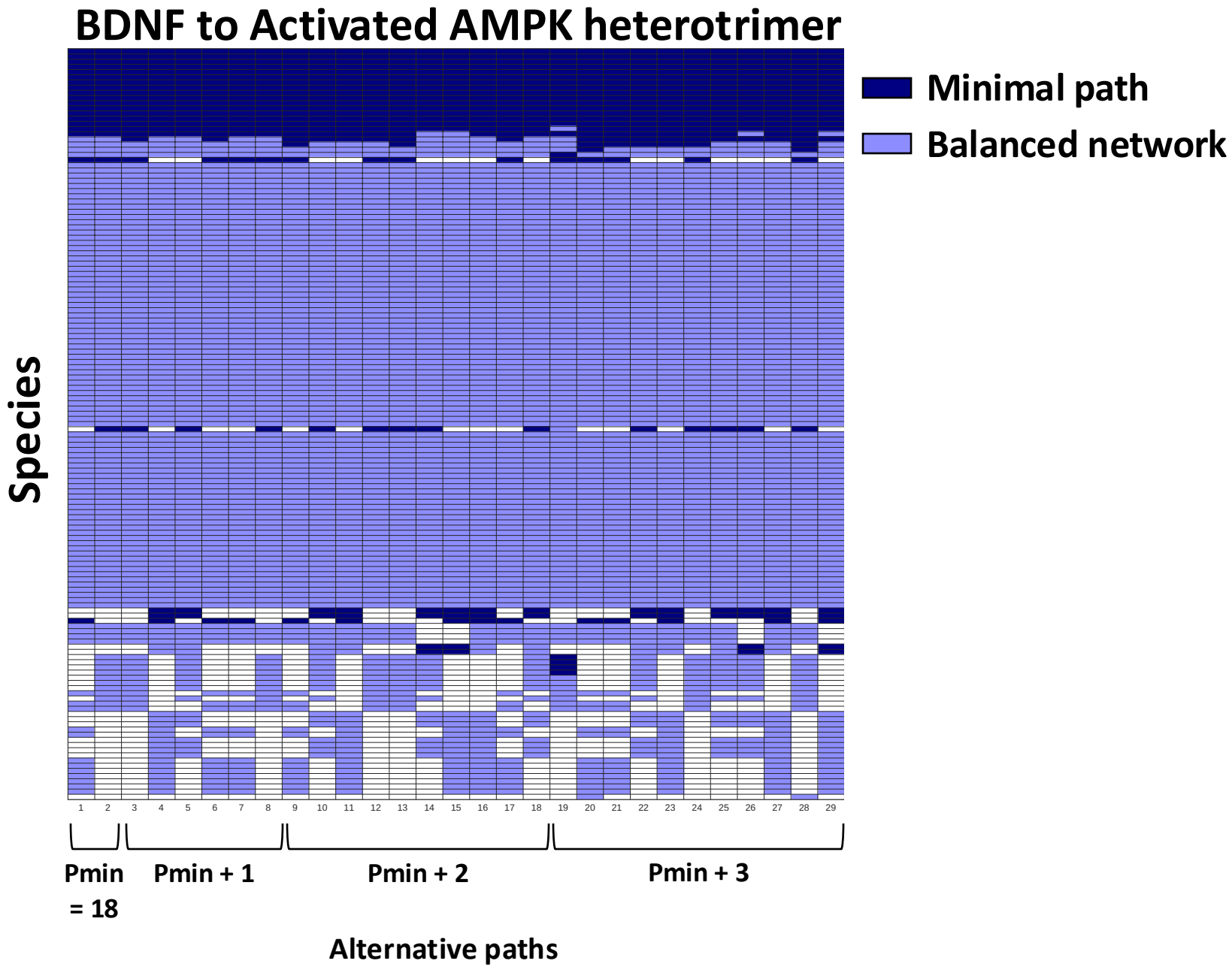
Studying BDNF connection to AMPK

Start	Target	Result	Min path
BDNF homodimer [e]	Activated AMPK heterotrimer [n]	YES	18
BDNF homodimer [e]	AMPK heterotrimer (active) [c]	NO	-
BDNF homodimer [e]	AMPK heterotrimer (inactive) [n]	NO	-
BDNF homodimer [e]	AMPK heterotrimer [c]	YES	21
BDNF homodimer [e]	AMPK heterotrimer:AMP [n]	NO	-
BDNF homodimer [e]	AMPK-alpha2:AMPK-beta:AMPK-gamma:AMP [c]	NO	-
BDNF homodimer [e]	p-AMPK heterotrimer [c]	YES	20
BDNF homodimer [e]	p-AMPK heterotrimer:AMP [c]	YES	21
BDNF homodimer [e]	p-AMPK heterotrimer:AMP [n]	YES	22
BDNF homodimer [e]	p-AMPK heterotrimer:AMP:p-S317,467,556,638,T575-ULK1: ATG13:RB1CC1:ATG101 [c]	YES	23
BDNF homodimer [e]	p-AMPK heterotrimer:AMP:p-T180,S317,467,556,638,T575-ULK1: ATG13:RB1CC1:ATG101 [c]	YES	24
BDNF homodimer [e]	p-AMPK heterotrimer:AMP:p-T180,S317,467,556,638,T575-ULK1: ATG13:RB1CC1:ATG101 [er]	YES	26
BDNF homodimer [e]	p-AMPK heterotrimer:AMP:p-T180,S317,467,556,638,T575-ULK1: p-ATG13:p-RB1CC1:ATG101 [c]	YES	25
BDNF homodimer [e]	p-AMPK heterotrimer:AMP:ULK1:ATG13:RB1CC1:ATG101 [c]	YES	22
BDNF homodimer [e]	SESN1,2,3:p-AMPK heterotrimer:AMP [c]	YES	17

Studying BDNF connection to AMPK

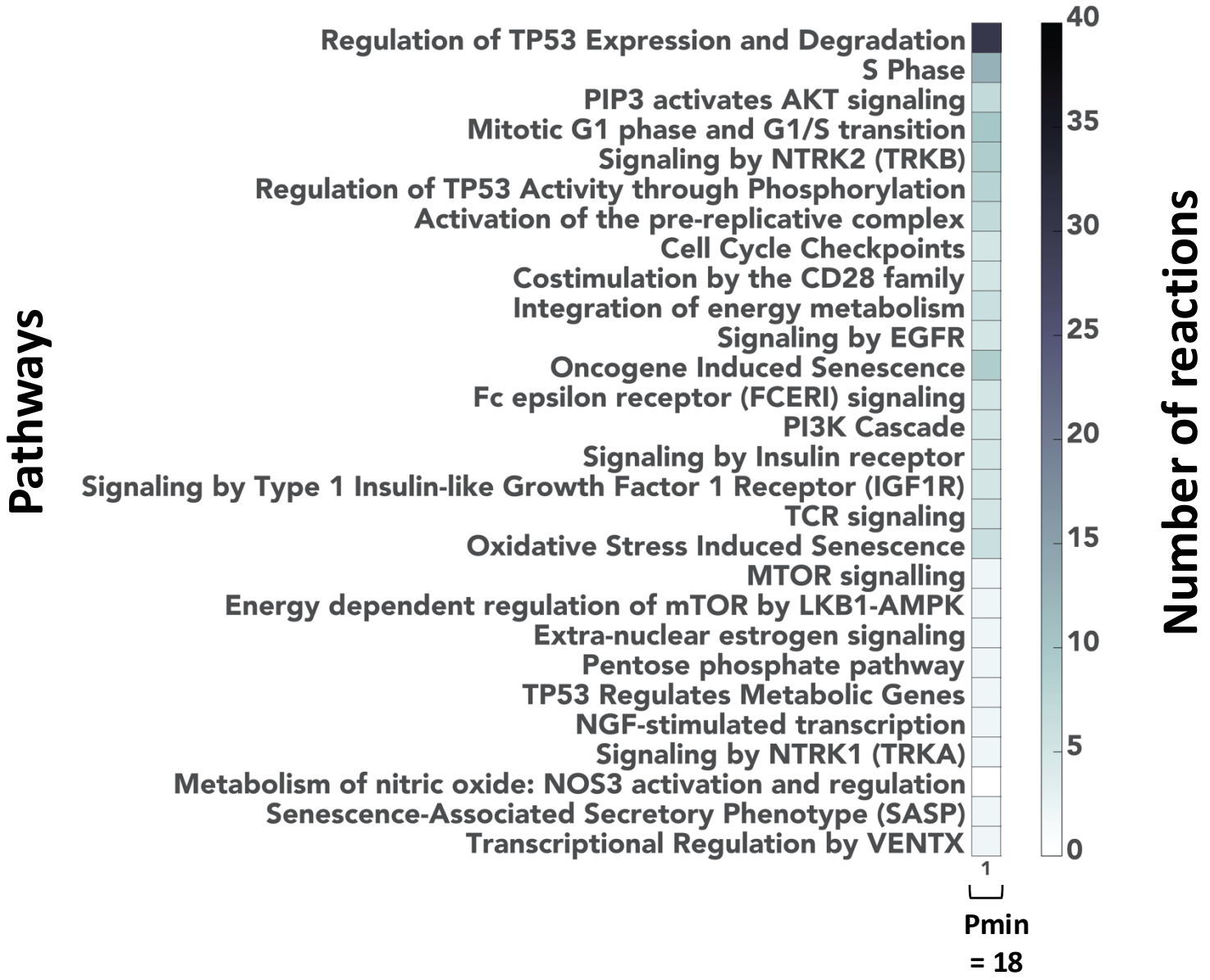


Studying BDNF connection to AMPK



Studying BDNF connection to AMPK

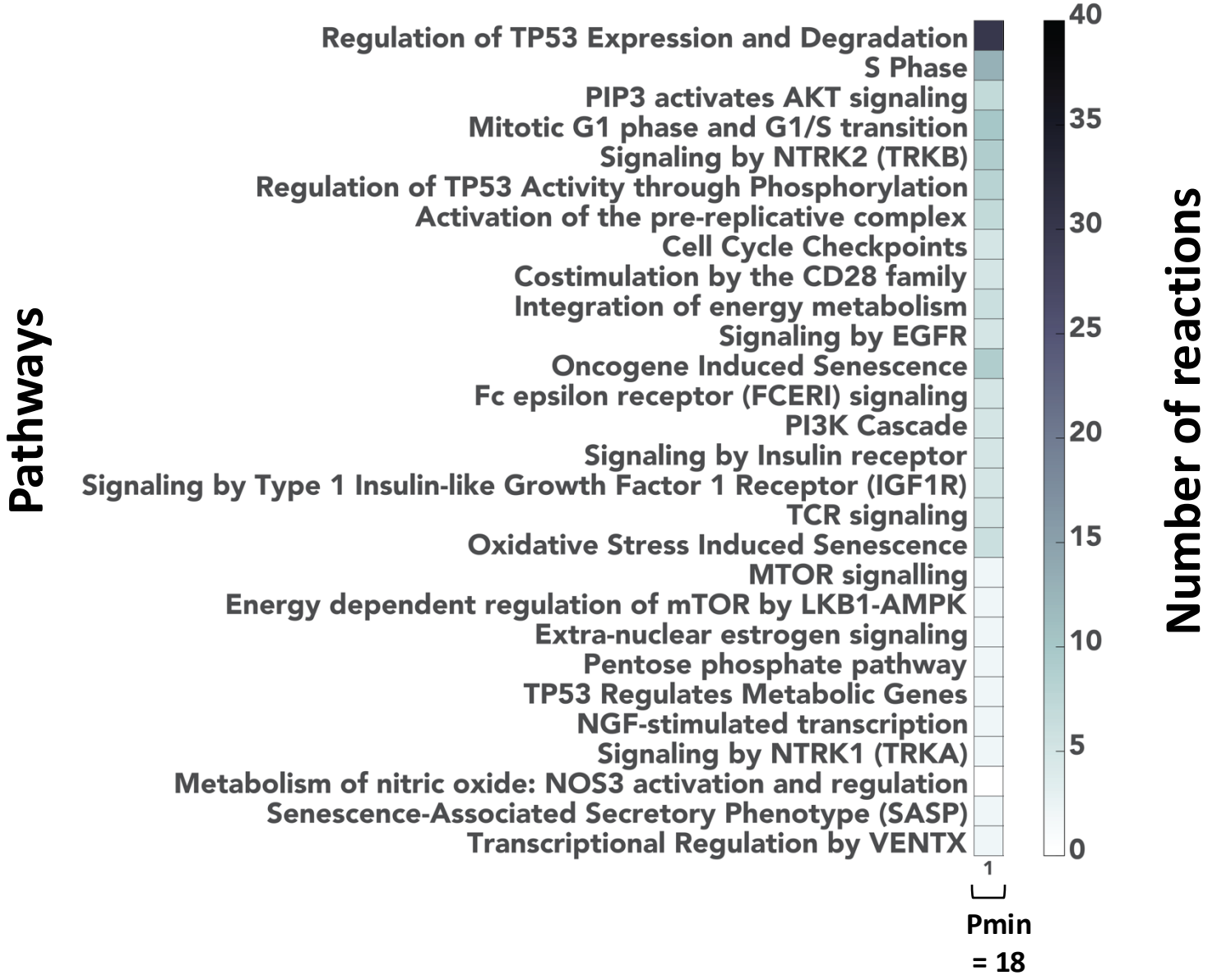
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK

Studying BDNF connection to AMPK

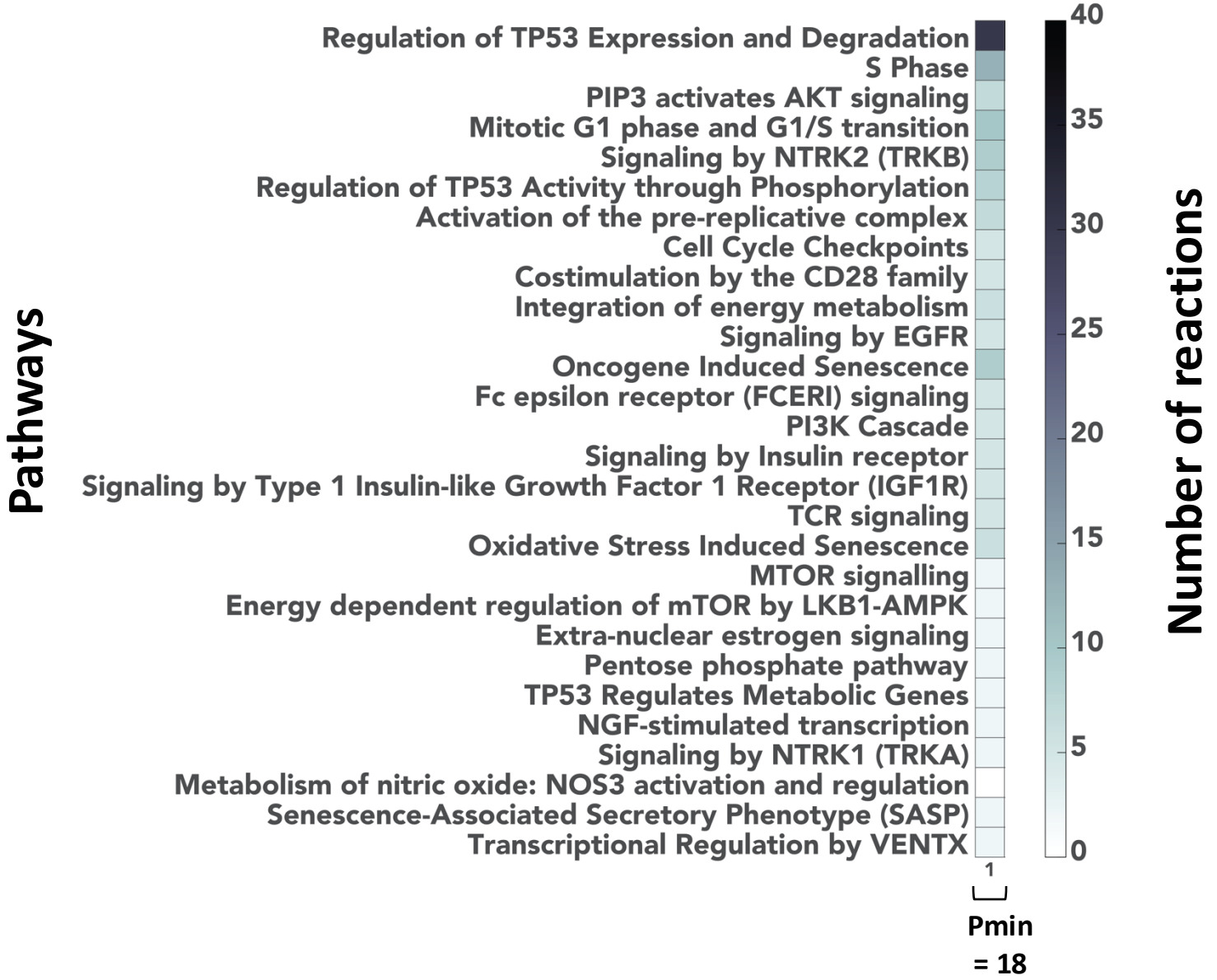
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK
- Total of 104 reactions (including the peripheral)

Studying BDNF connection to AMPK

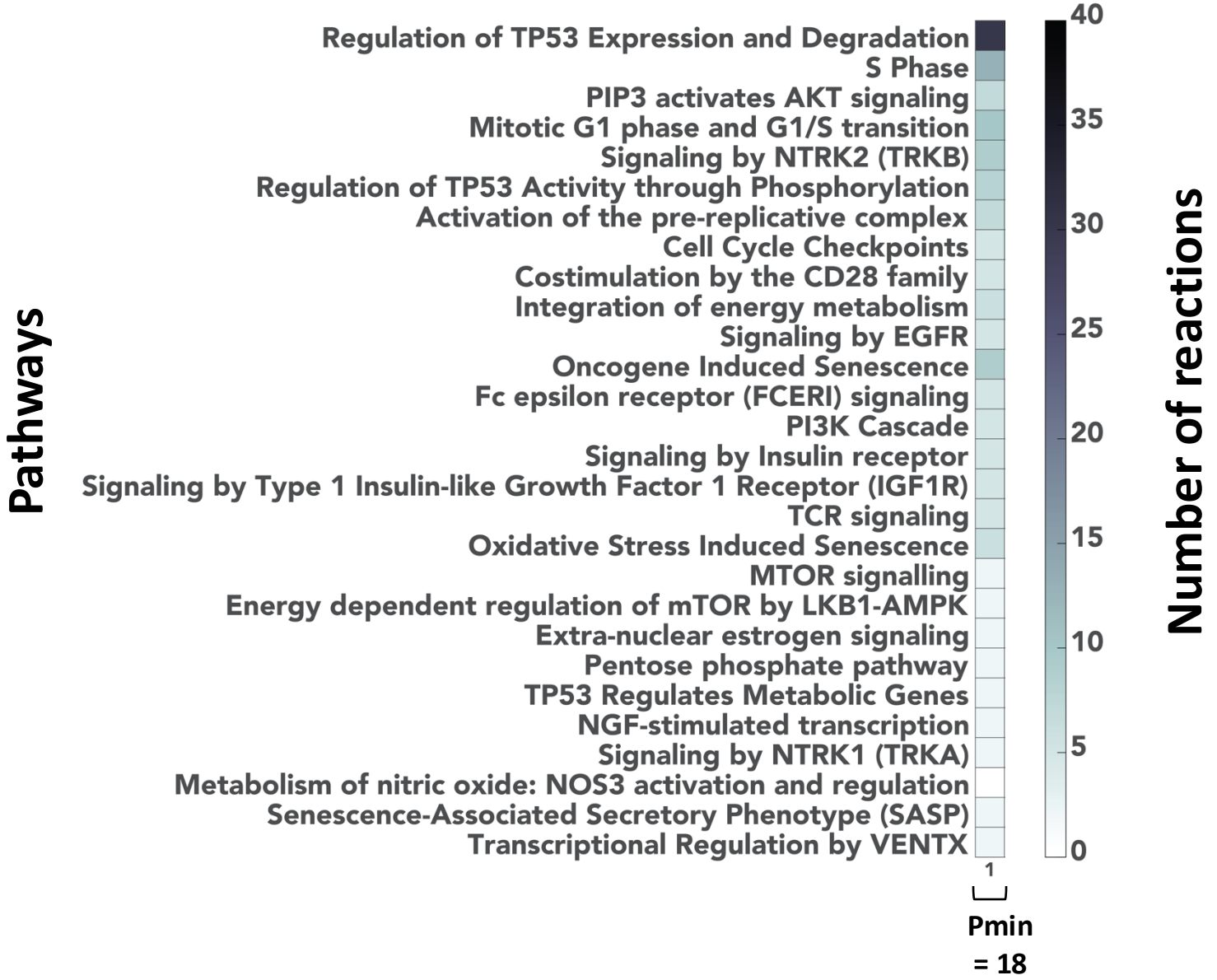
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK
- Total of 104 reactions (including the peripheral)
- These 104 reactions from 27 pathways

Studying BDNF connection to AMPK

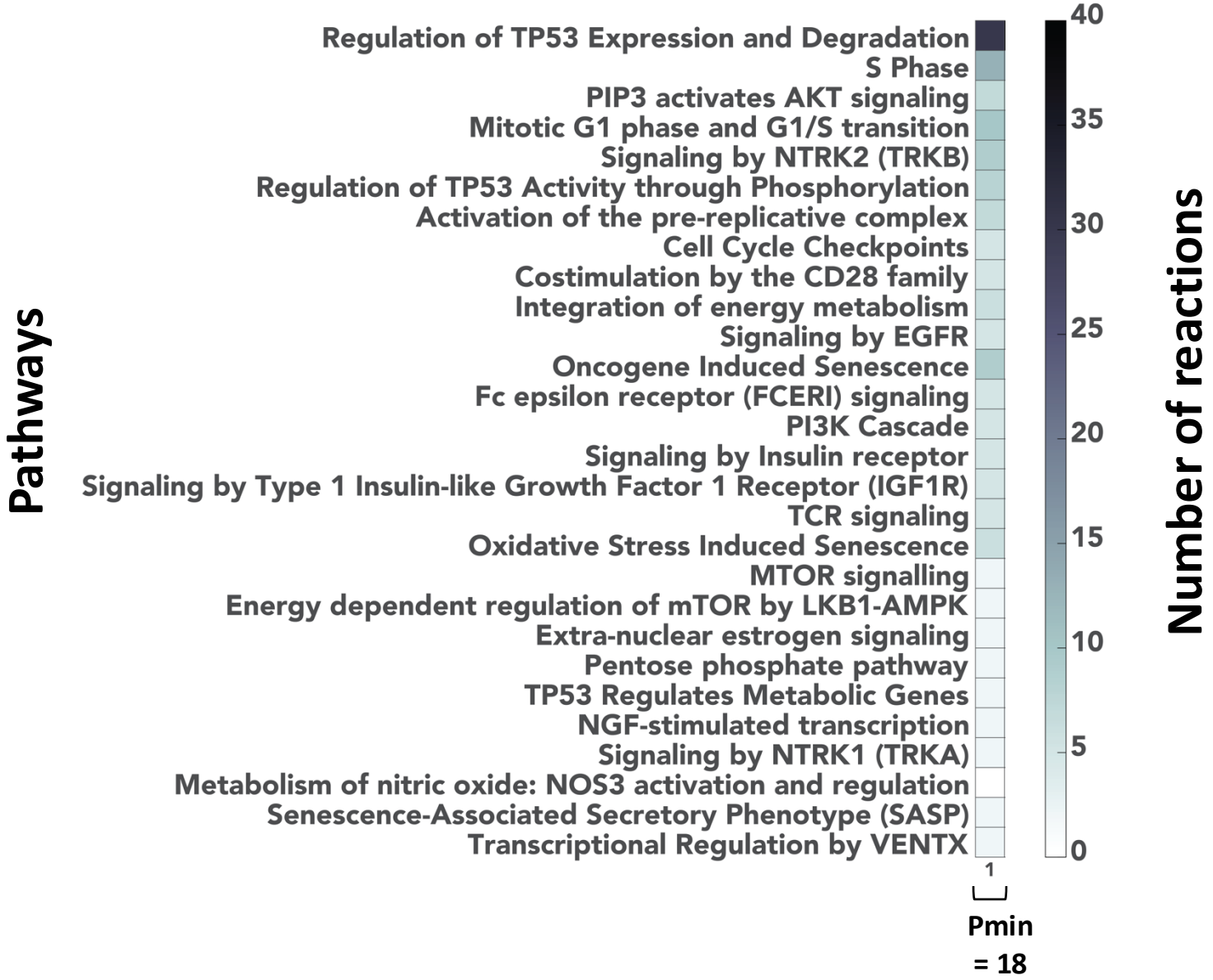
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK
- Total of 104 reactions (including the peripheral)
- These 104 reactions from 27 pathways
- Max of 30 reactions in Regulation of TP53

Studying BDNF connection to AMPK

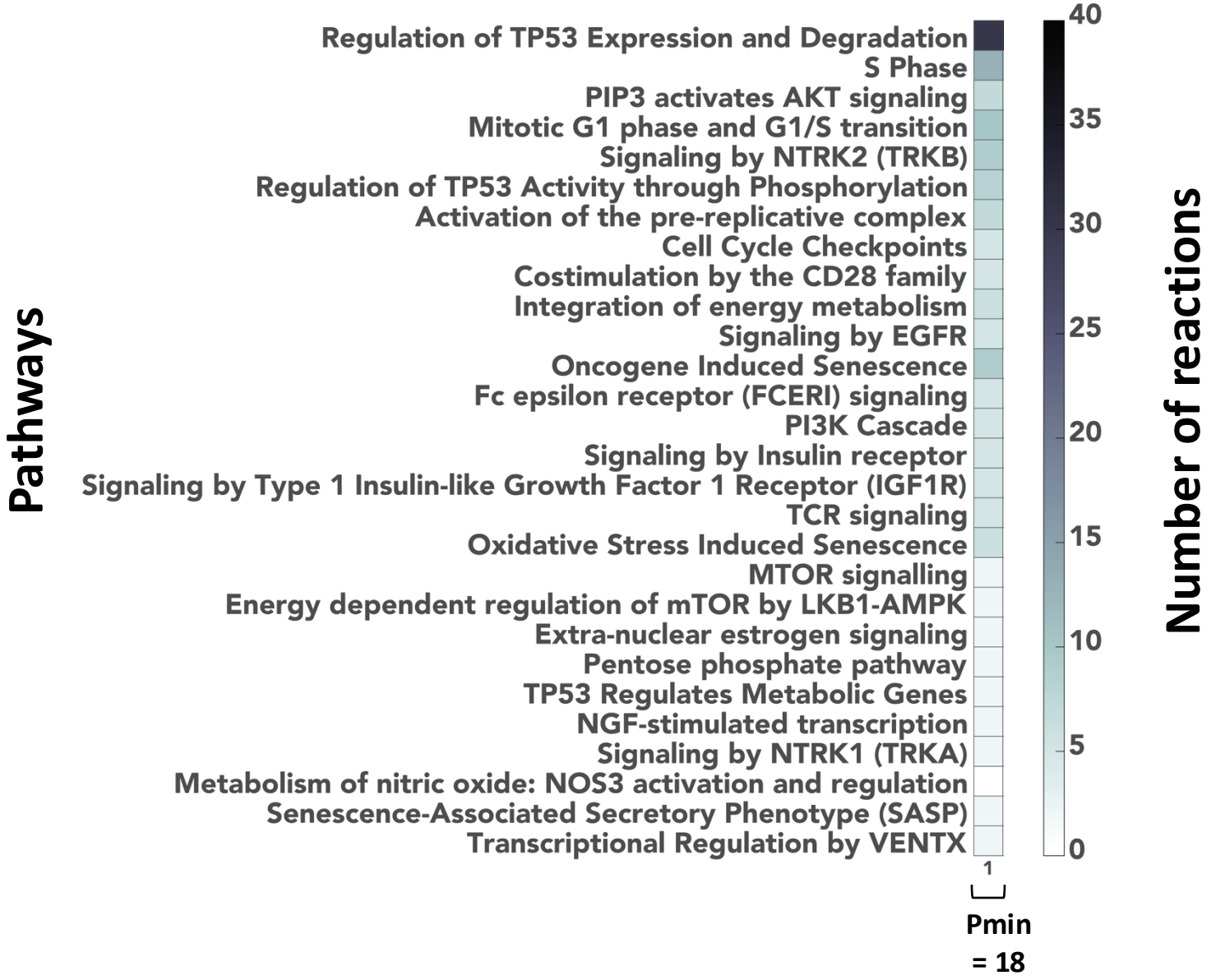
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK
- Total of 104 reactions (including the peripheral)
- These 104 reactions from 27 pathways
- Max of 30 reactions in Regulation of TP53
- Min of 2 reactions in 9 pathways

Studying BDNF connection to AMPK

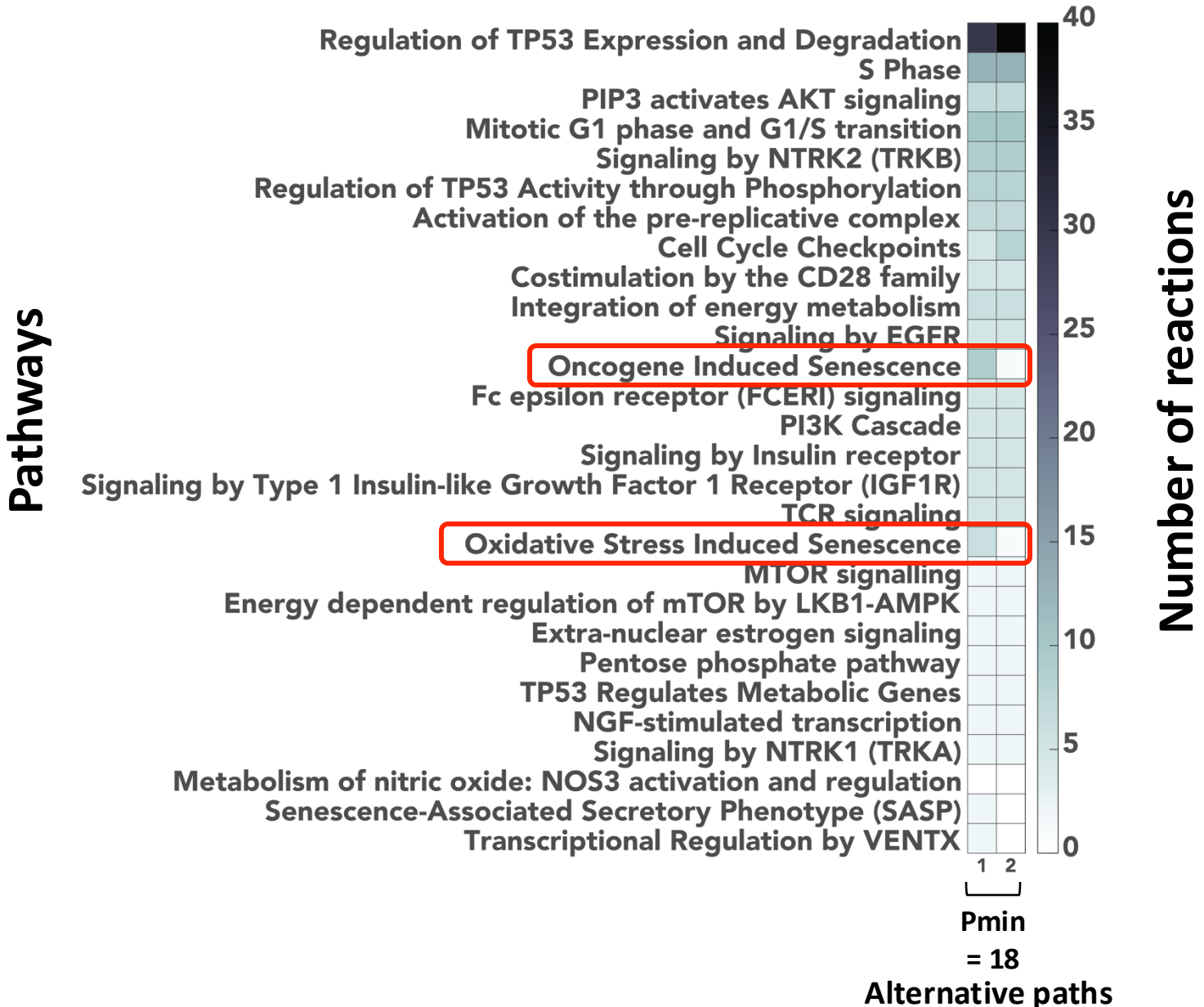
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK
- Total of 104 reactions (including the peripheral)
- These 104 reactions from 27 pathways
- Max of 30 reactions in Regulation of TP53
- Min of 2 reactions in 9 pathways
- Metabolism of nitric oxide does not participate in this path

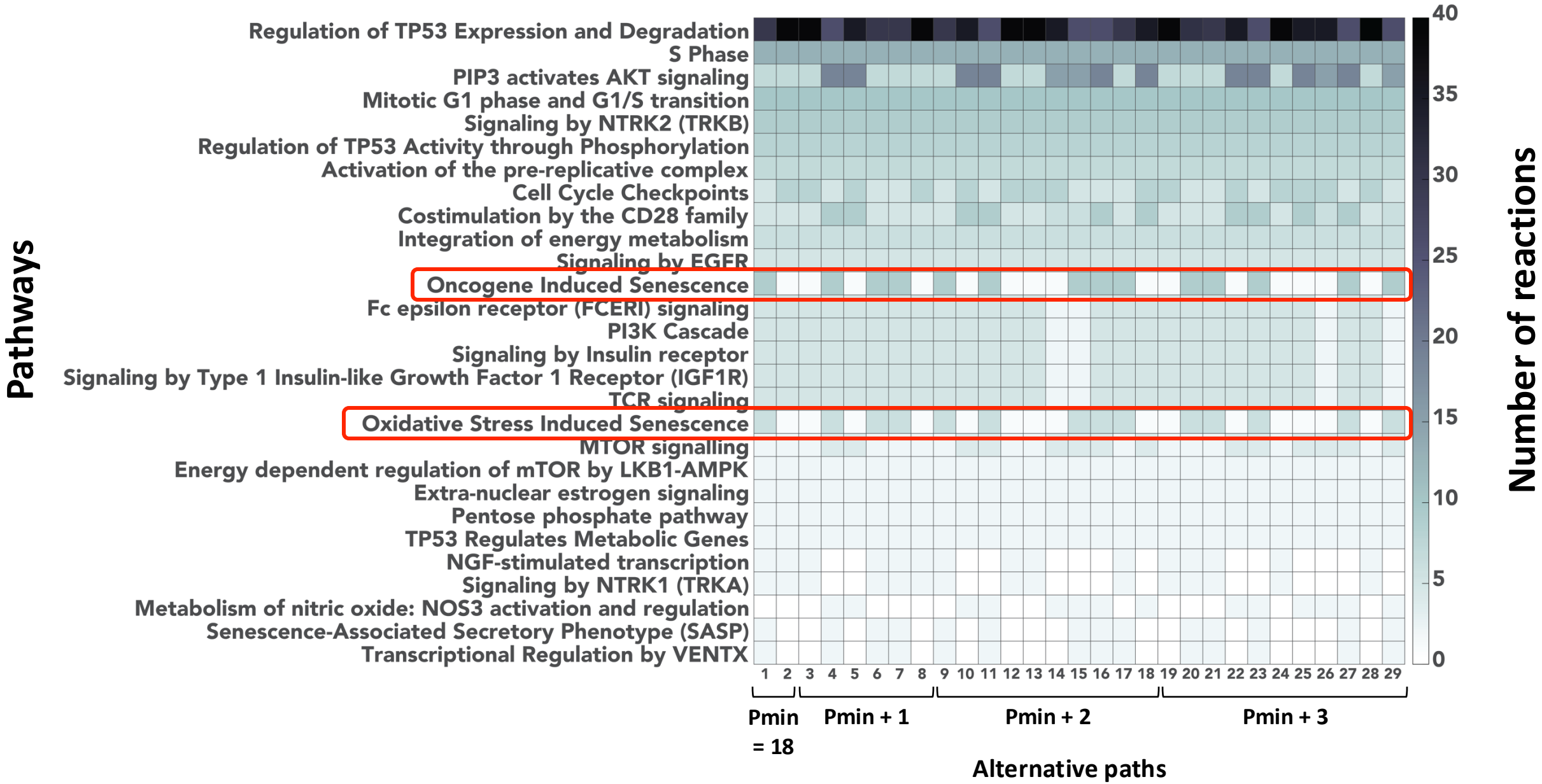
Studying BDNF connection to AMPK

BDNF to Activated AMPK heterotrimer



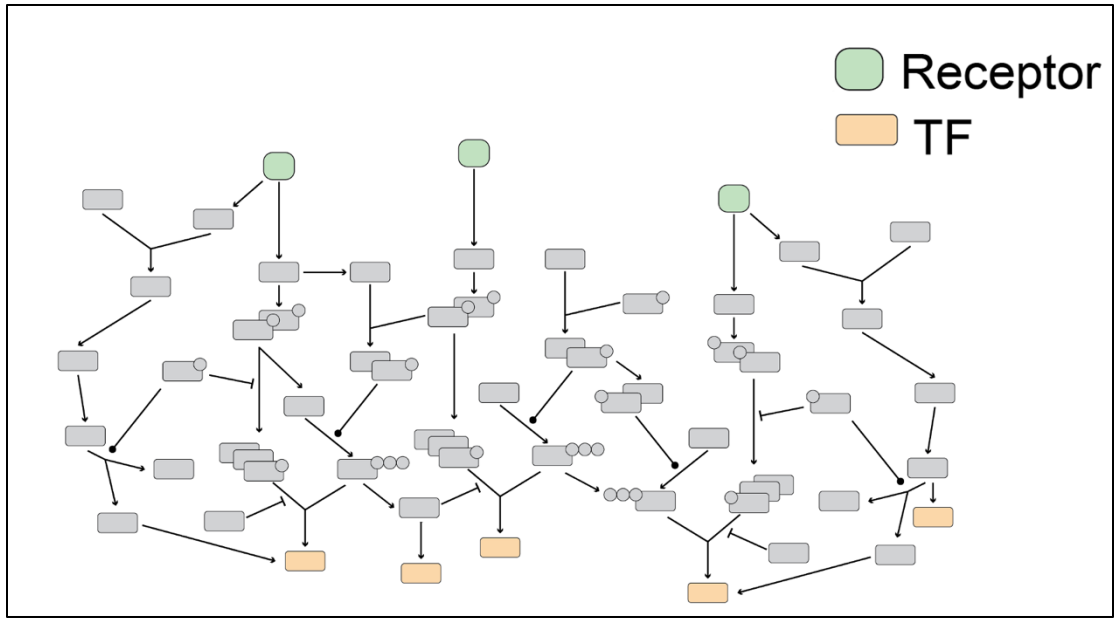
Studying BDNF connection to AMPK

BDNF to Activated AMPK heterotrimer



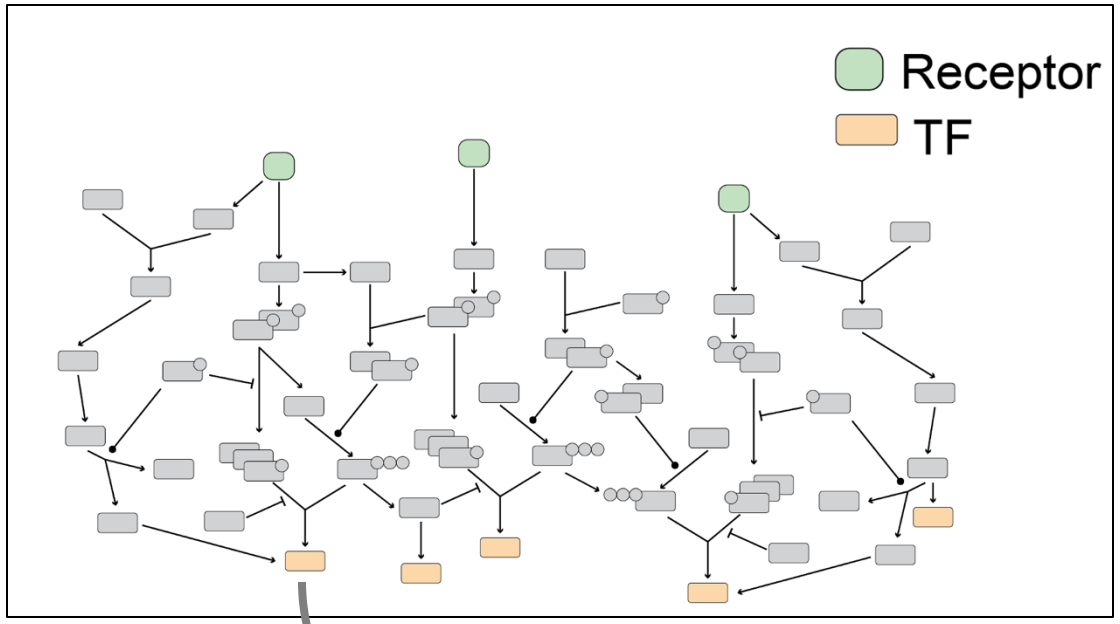
Connecting signaling to metabolism

Signaling network

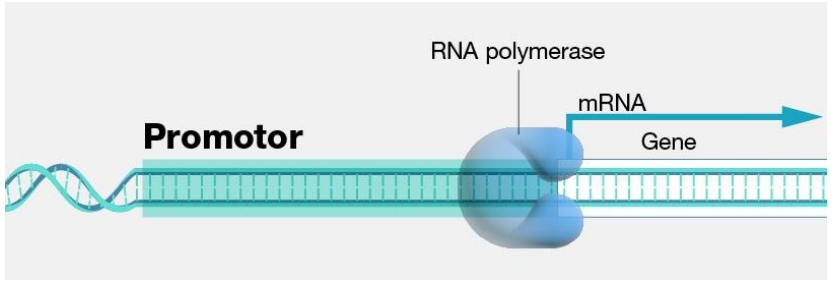


Connecting signaling to metabolism

Signaling network

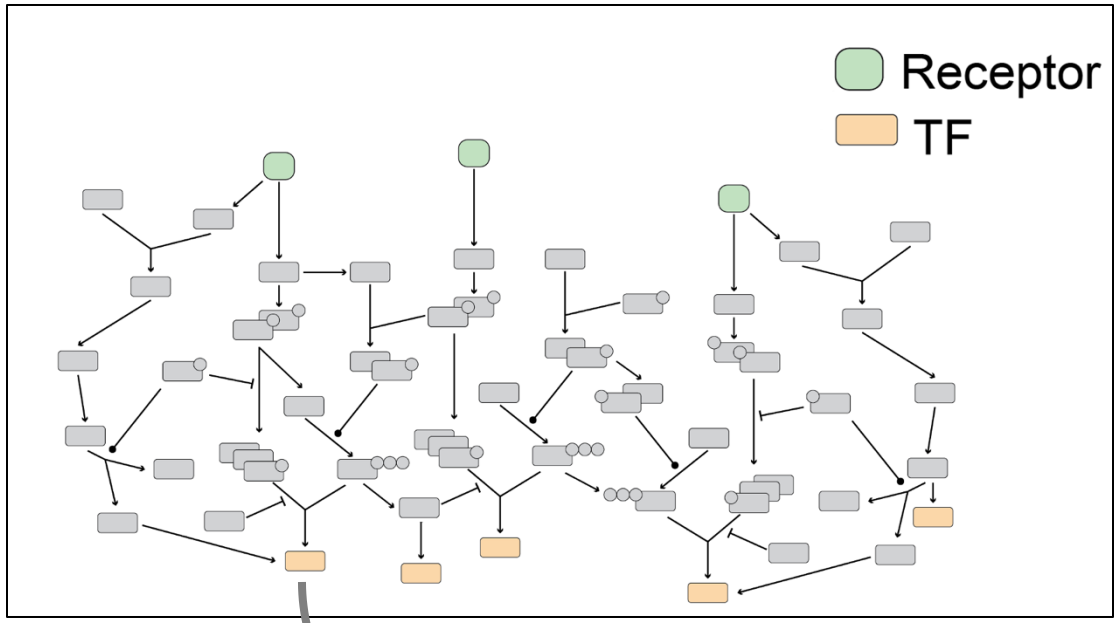


Gene expression

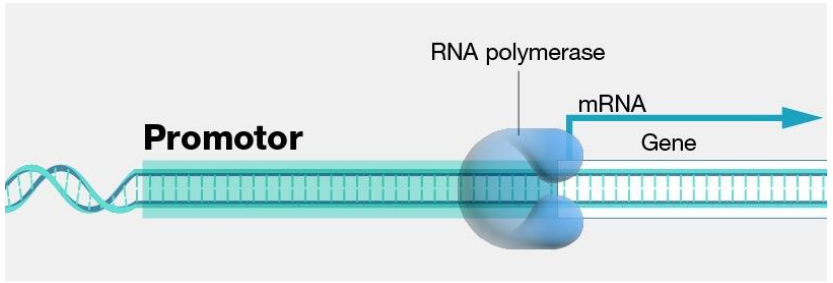


Connecting signaling to metabolism

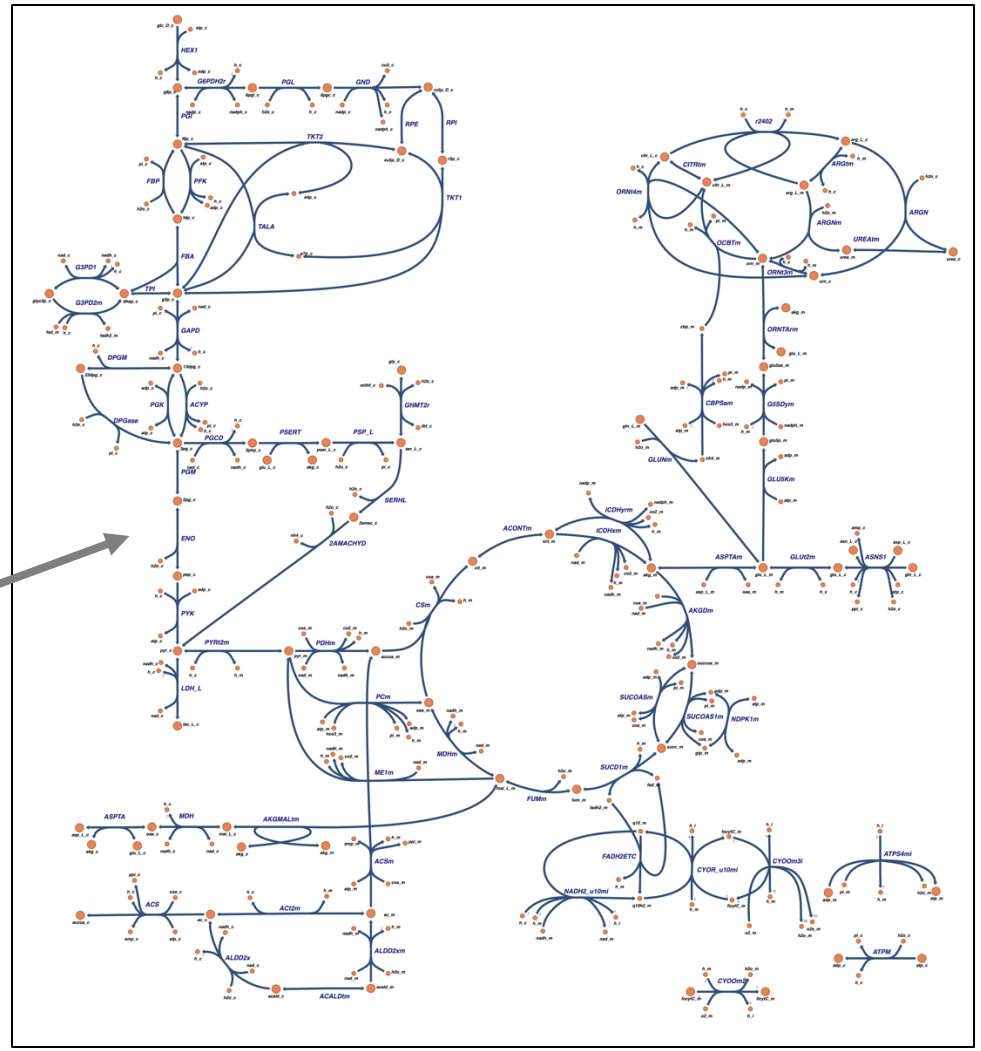
Signaling network



Gene expression



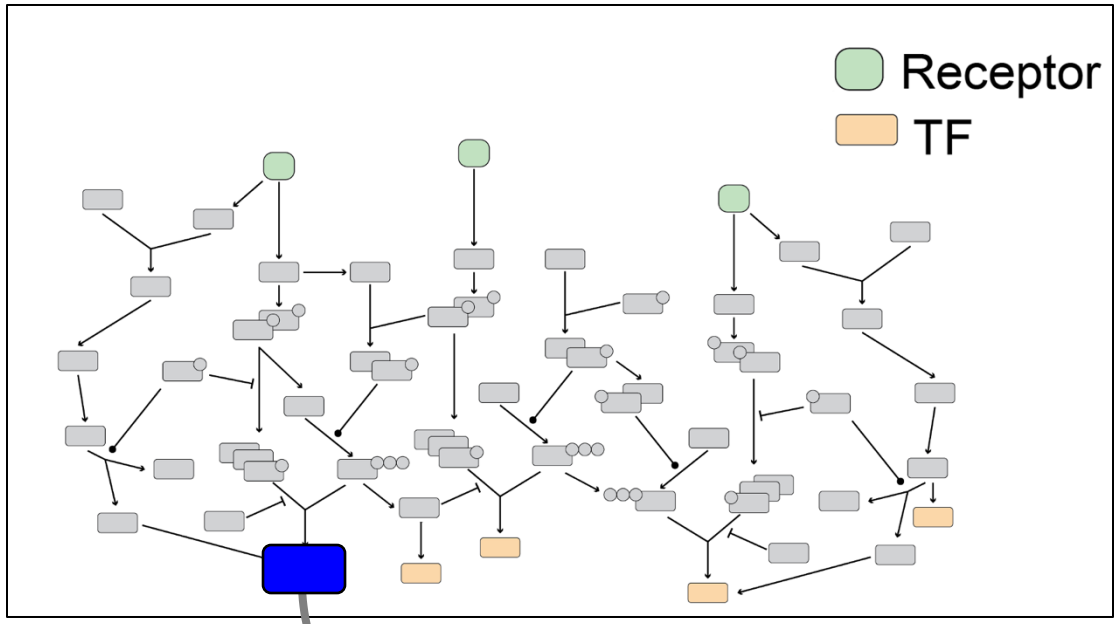
Metabolic network



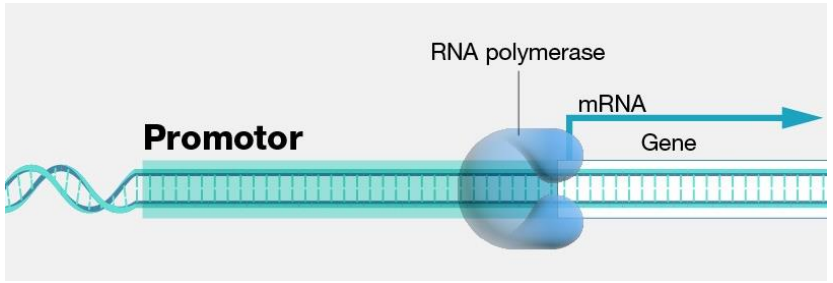
*** 115 TFs in Recon3D**

Connecting signaling to metabolism

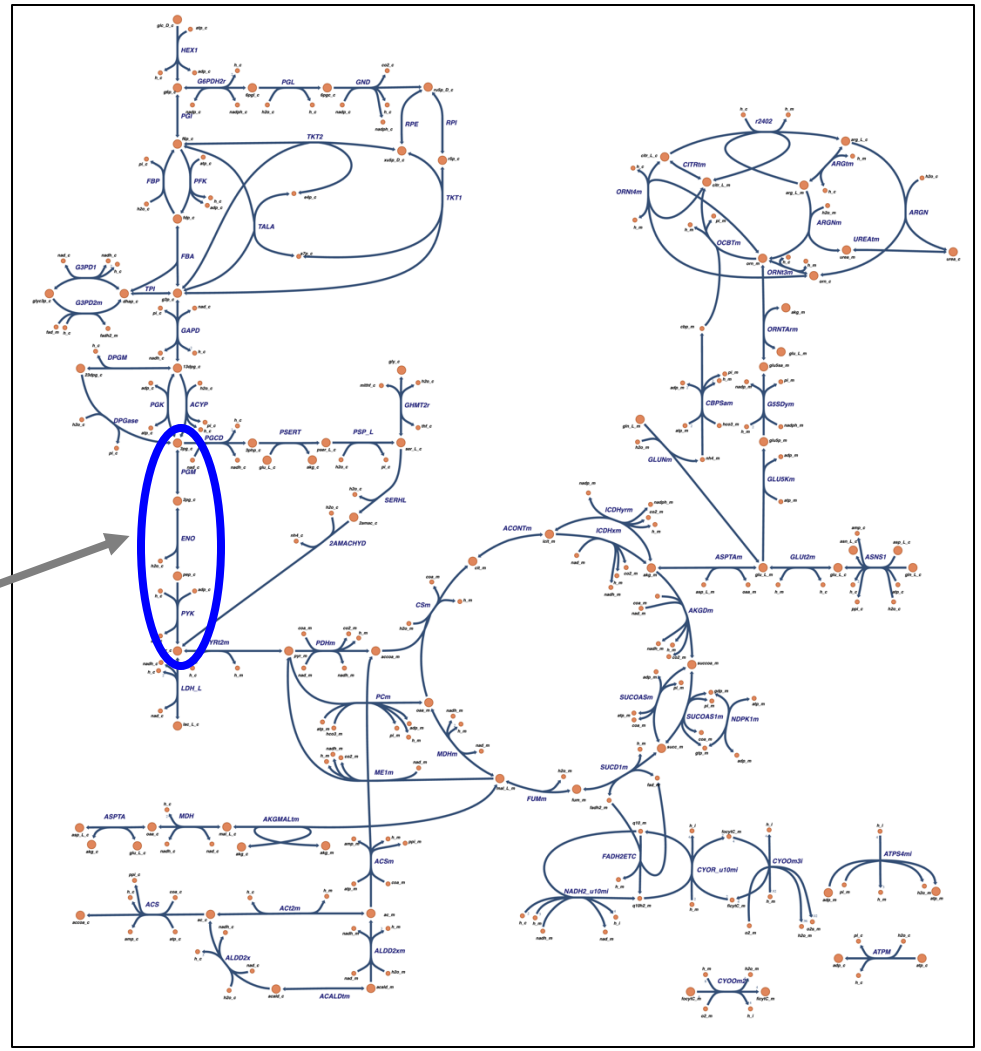
Signaling network



Gene expression

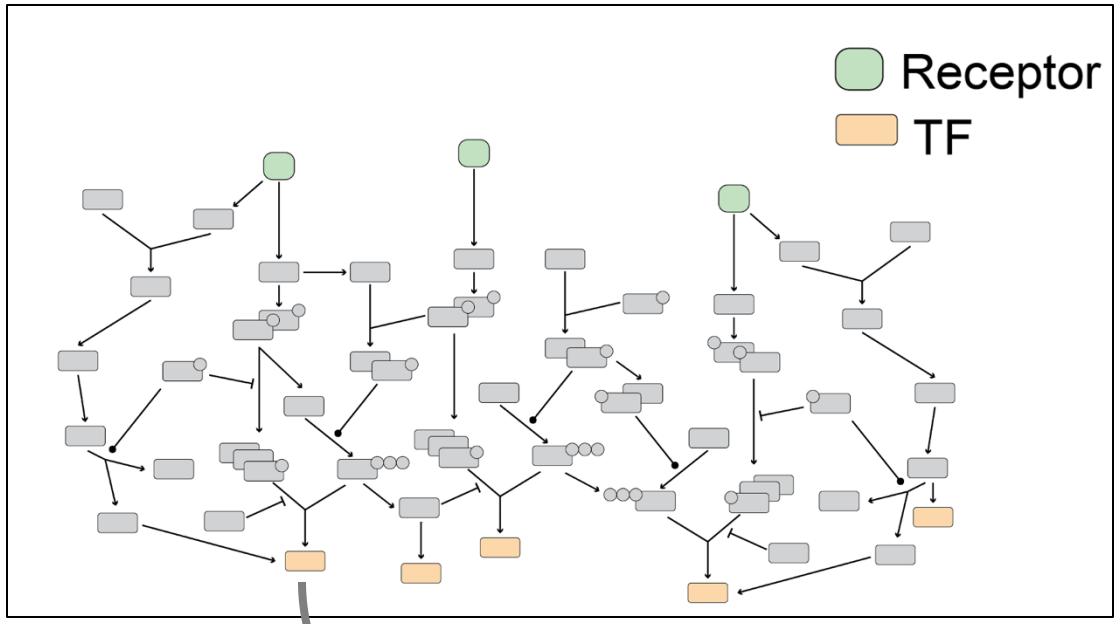


Metabolic network

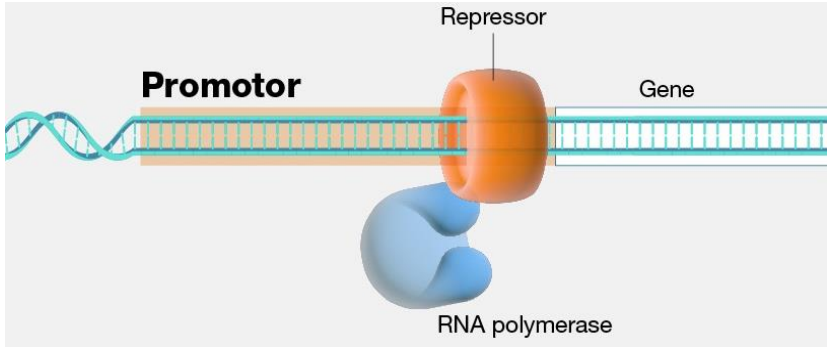


Connecting signaling to metabolism

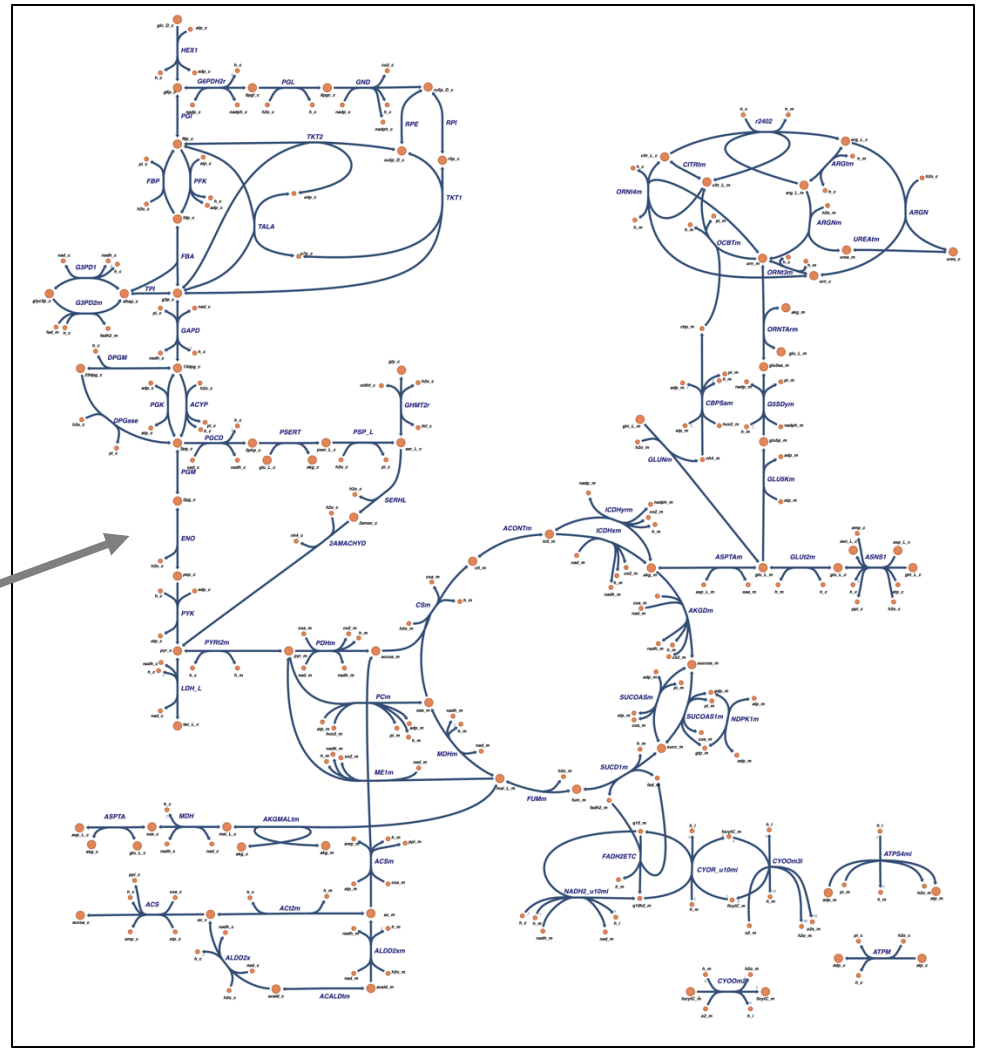
Signaling network



Gene expression

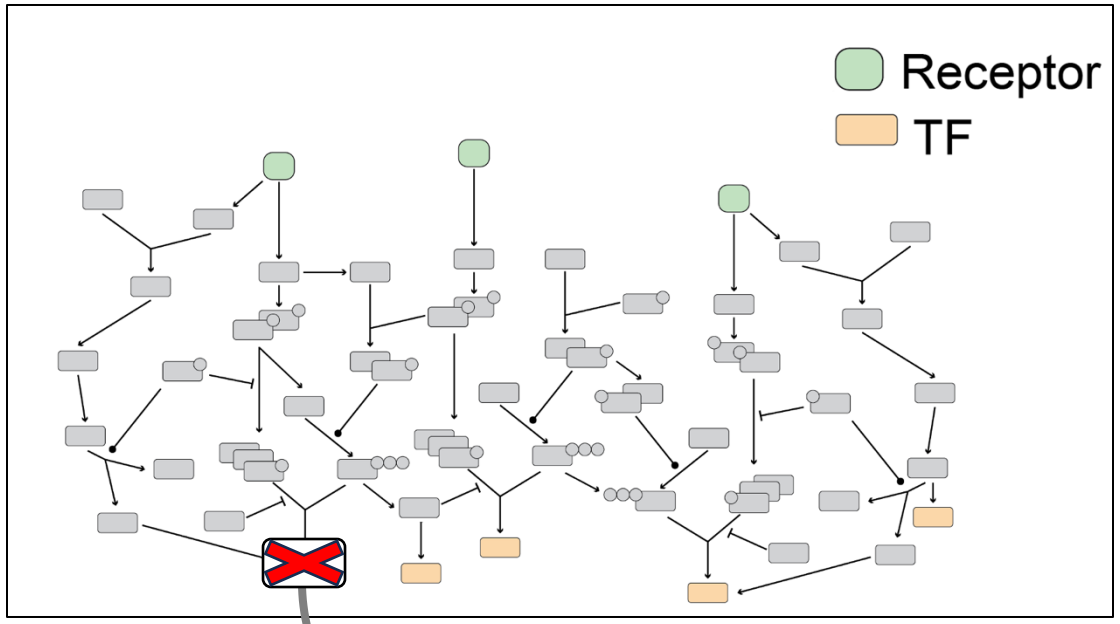


Metabolic network

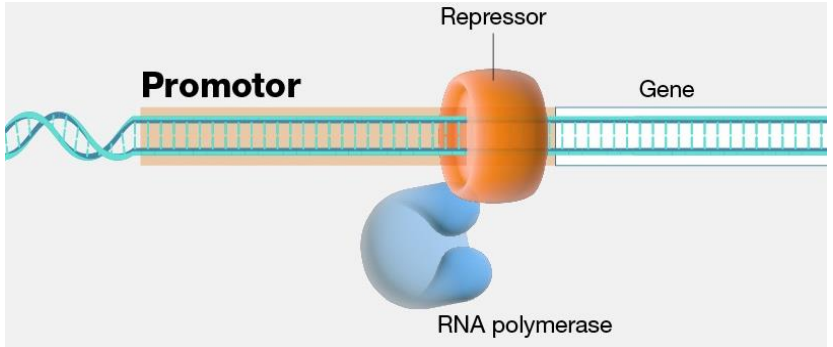


Connecting signaling to metabolism

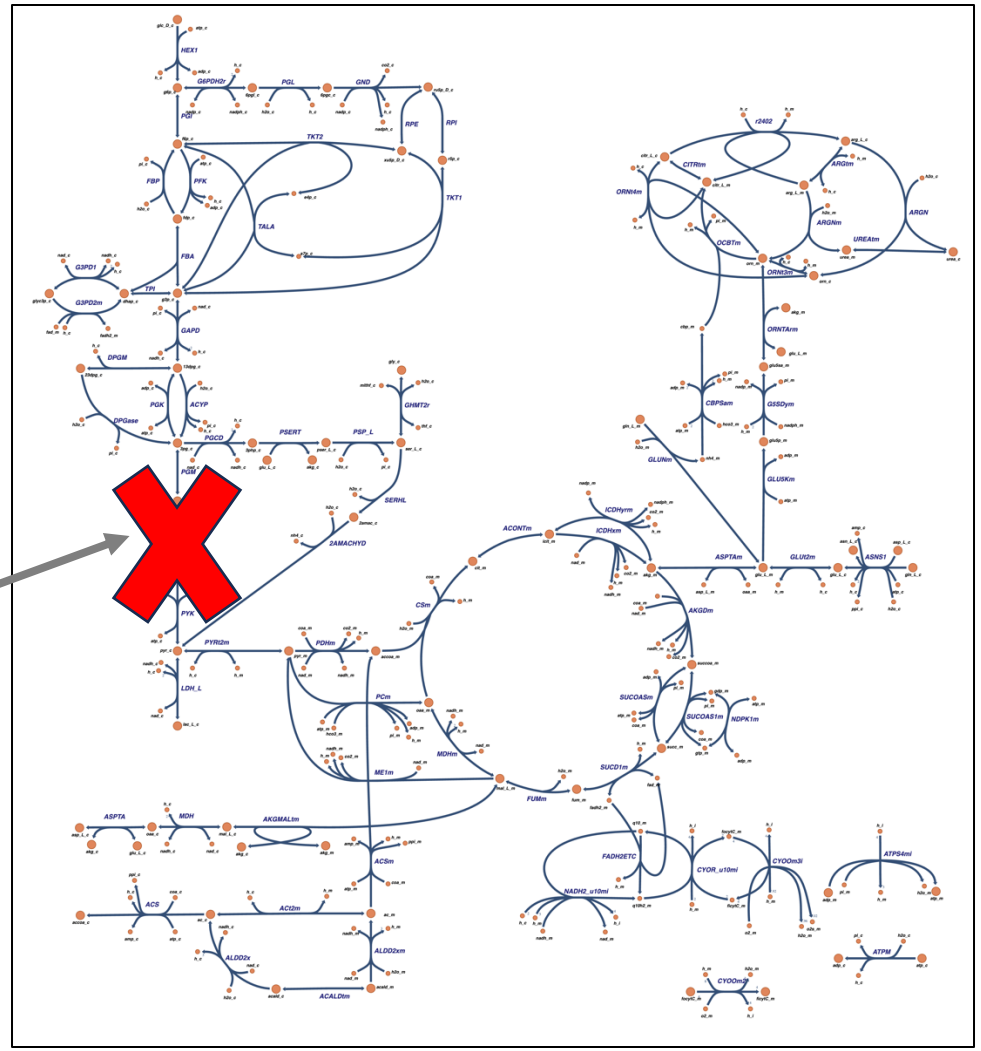
Signaling network



Gene expression



Metabolic network



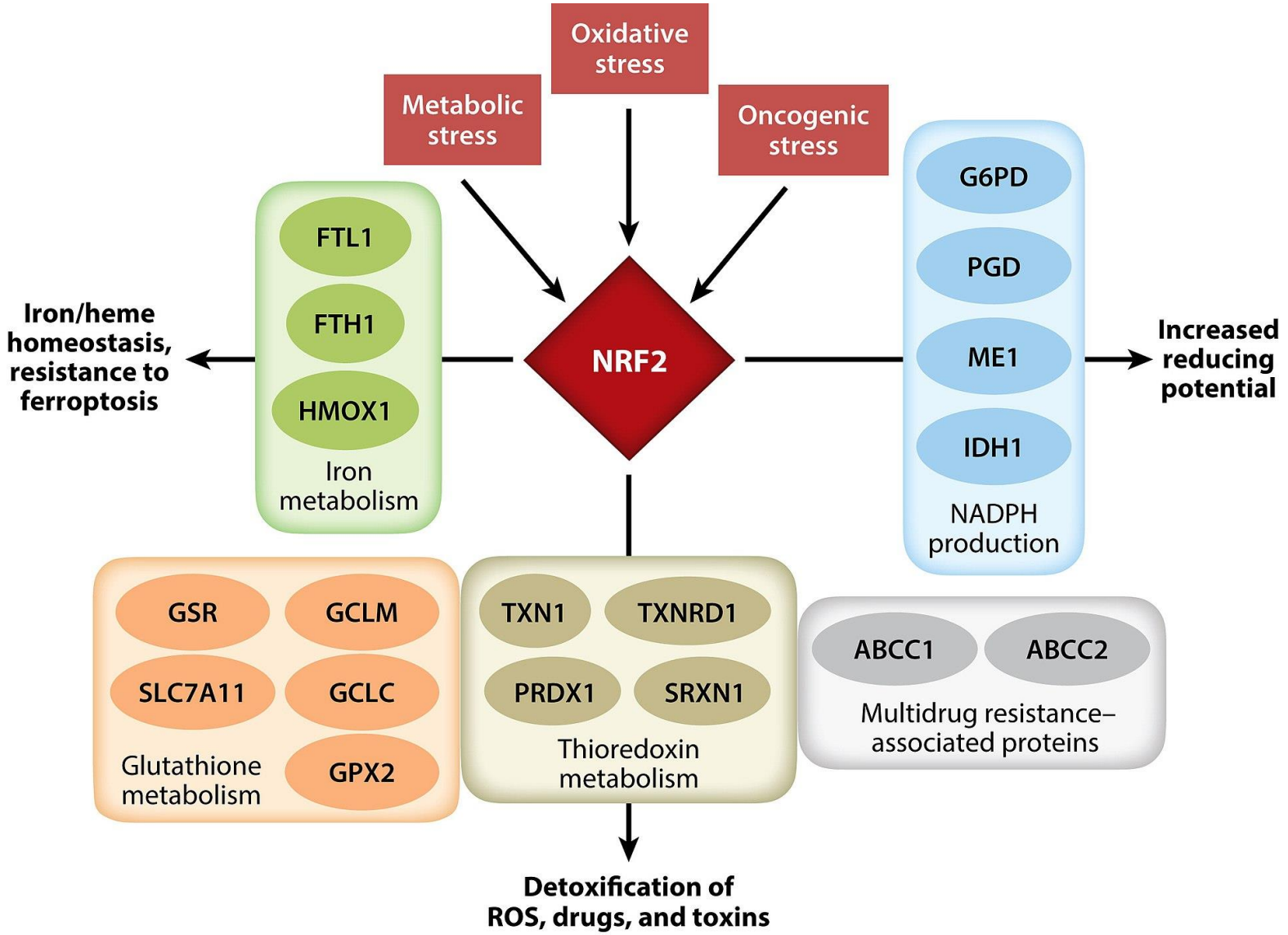
From ligand to transcription factor

From BDNF to NFE2L (NRF2) transcription factor

Transcription factor	Gene
p-NFE2L2 [n]	GSR
	GSTA3
	HMOX1
	IDH1
	ME1
	PRDX1
	SRXN1
	TALDO1
	TKT
p-AcK-NFE2L2:CREBBP, EP300 [n]	G6PD
	GCLC
	GCLM
	GSTA1
	NQO1
	PGD
	SLC7A11
	TXNRD1
p-NFE2L2:MAFK [n]	HMOX1

From ligand to transcription factor

From BDNF to NFE2L (NRF2) transcription factor



Wu WL, Papagiannakopoulos T. 2020. *Annu. Rev. Cancer Biol.* 4:413–35

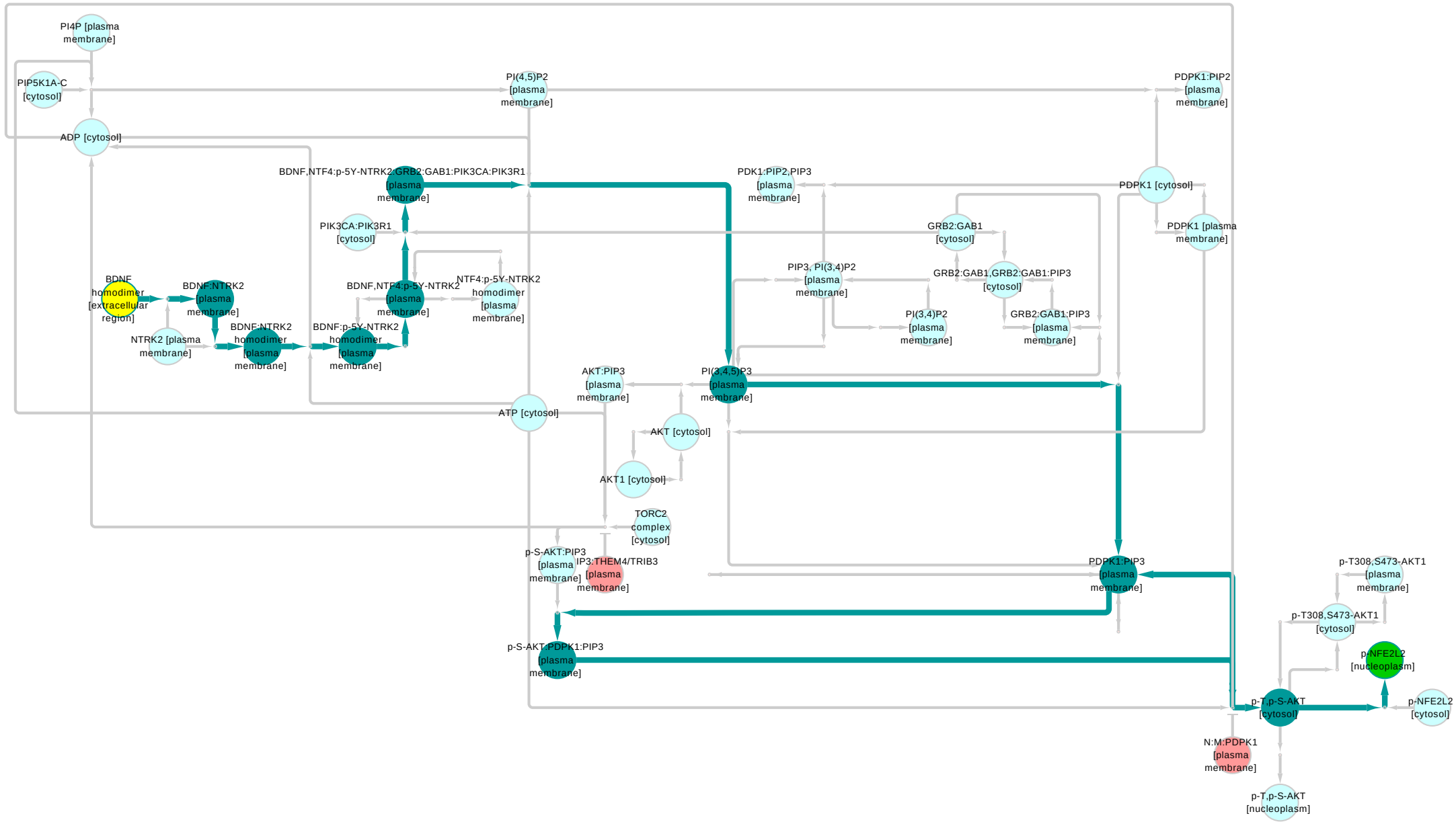
From ligand to transcription factor

Start	Target	Result	Min path
BDNF homodimer [e]	p-NFE2L2 [n]	YES	10
BDNF homodimer [e]	p-AcK-NFE2L2:CREBBP, EP300 [n]	YES	12
BDNF homodimer [e]	p-NFE2L2:MAFK [n]	YES	11

From ligand to transcription factor

Start	Target	Result	Min path
BDNF homodimer [e]	p-NFE2L2 [n]	YES	10
BDNF homodimer [e]	p-AcK-NFE2L2:CREBBP, EP300 [n]	YES	12
BDNF homodimer [e]	p-NFE2L2:MAFK [n]	YES	11

From ligand to transcription factor



Perspectives

- **Explore signaling-metabolism interaction**

Perspectives

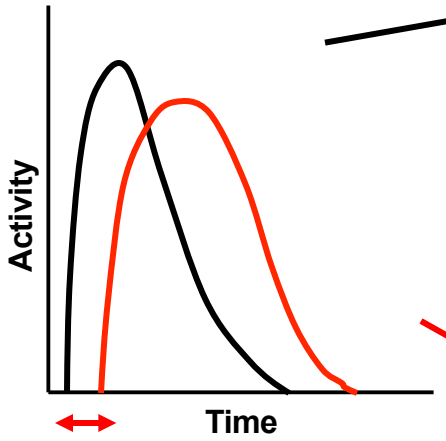
- **Explore signaling-metabolism interaction**
- **Expand multi-omics data integration (condition-specific signaling models, information flows deregulation)**

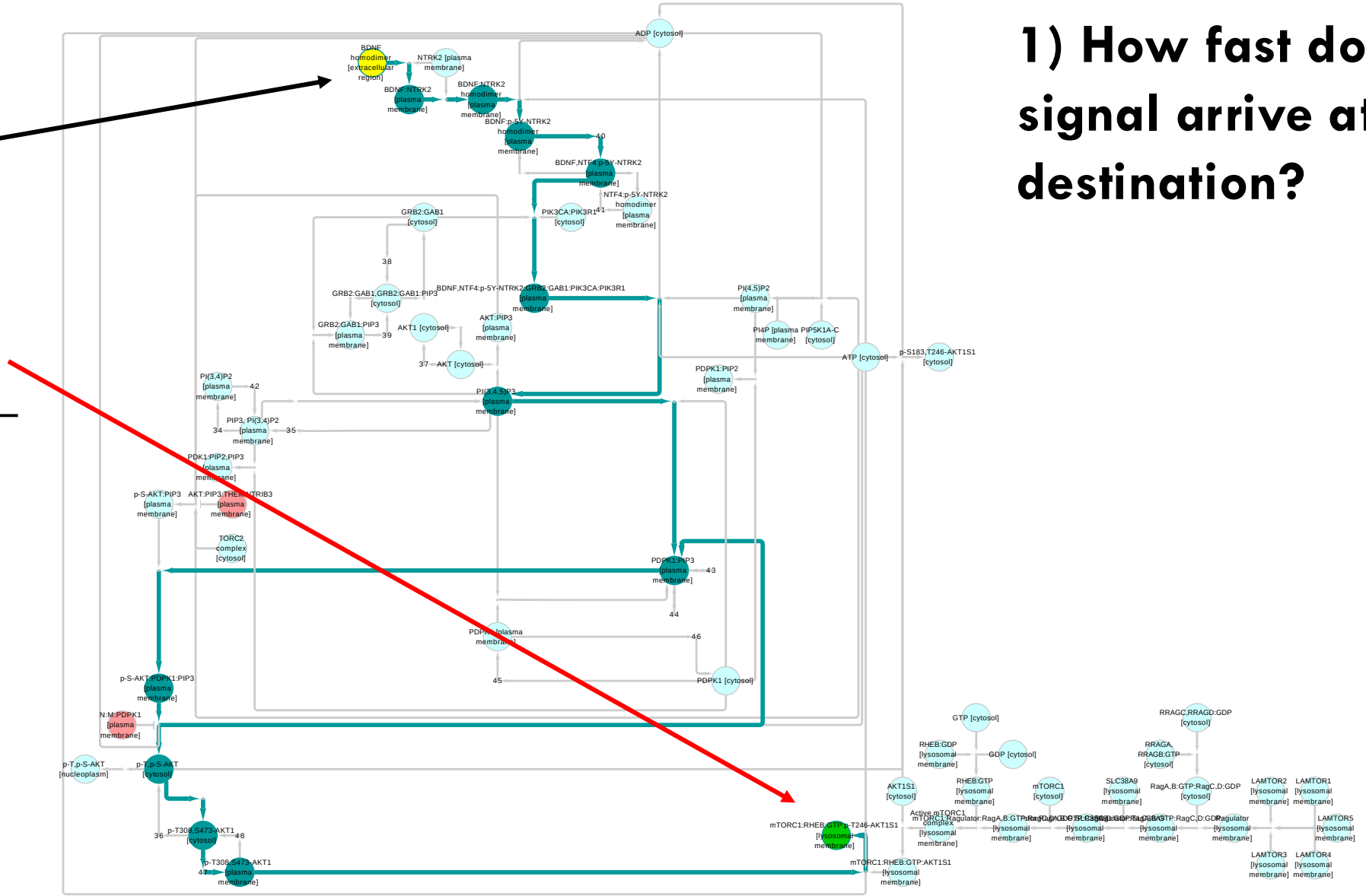
Perspectives

- **Explore signaling-metabolism interaction**
- **Expand multi-omics data integration (condition-specific signaling models, information flows deregulation)**
- **Create dynamical signaling models**

Perspectives

Create dynamical signaling models

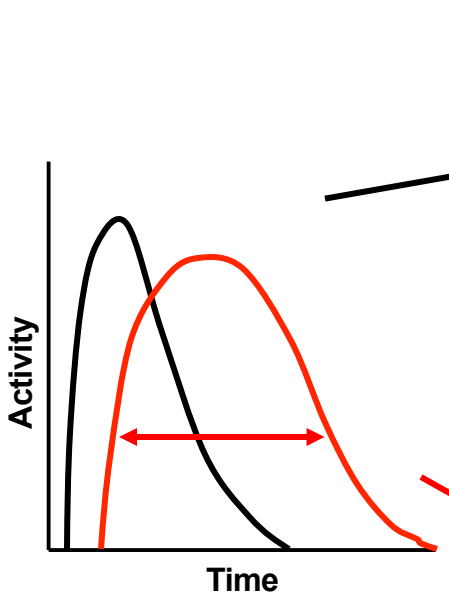


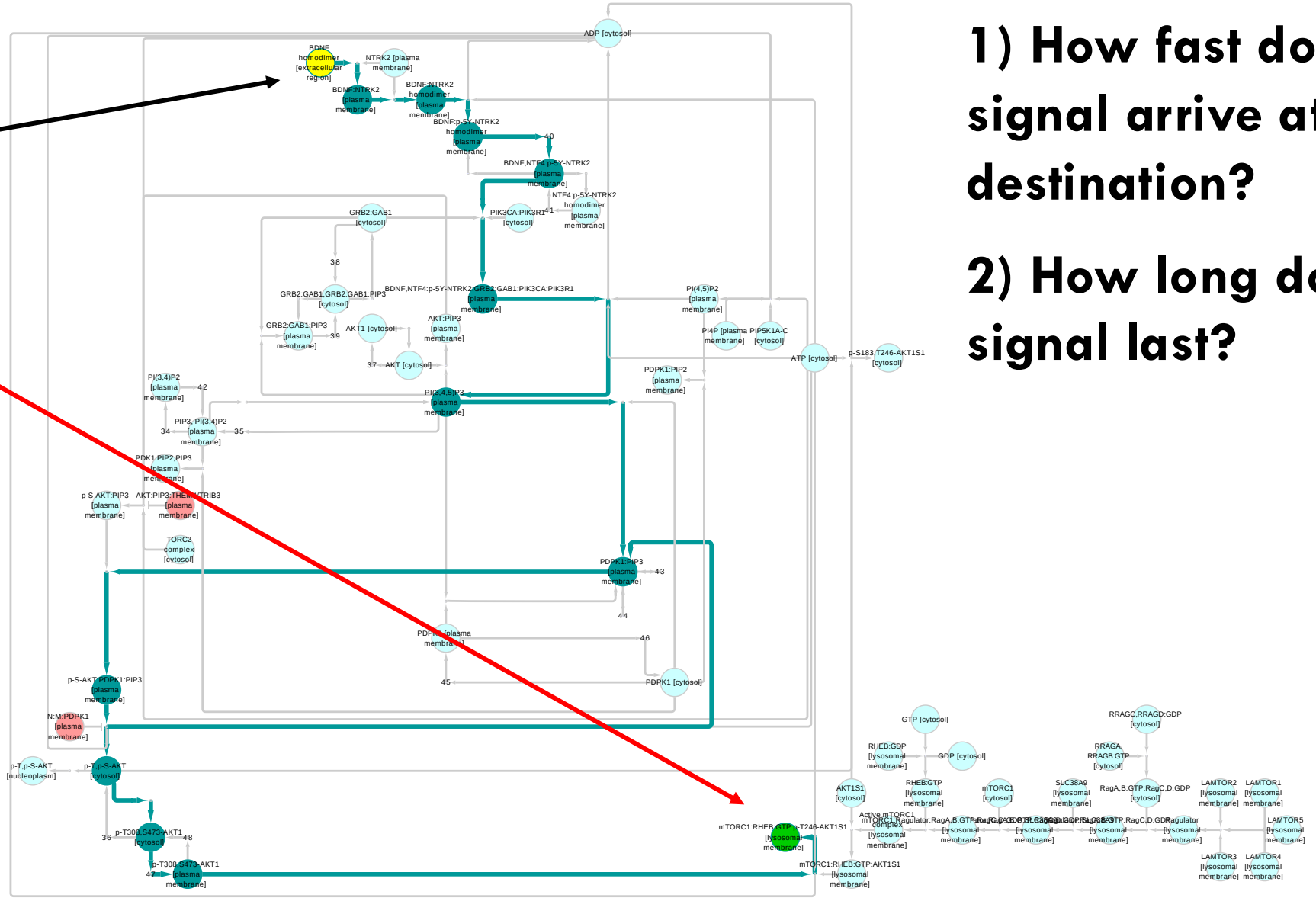


1) How fast does the signal arrive at its destination?

Perspectives

Create dynamical signaling models



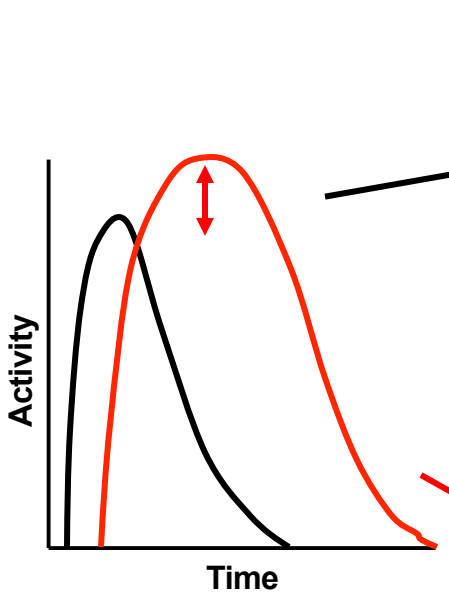


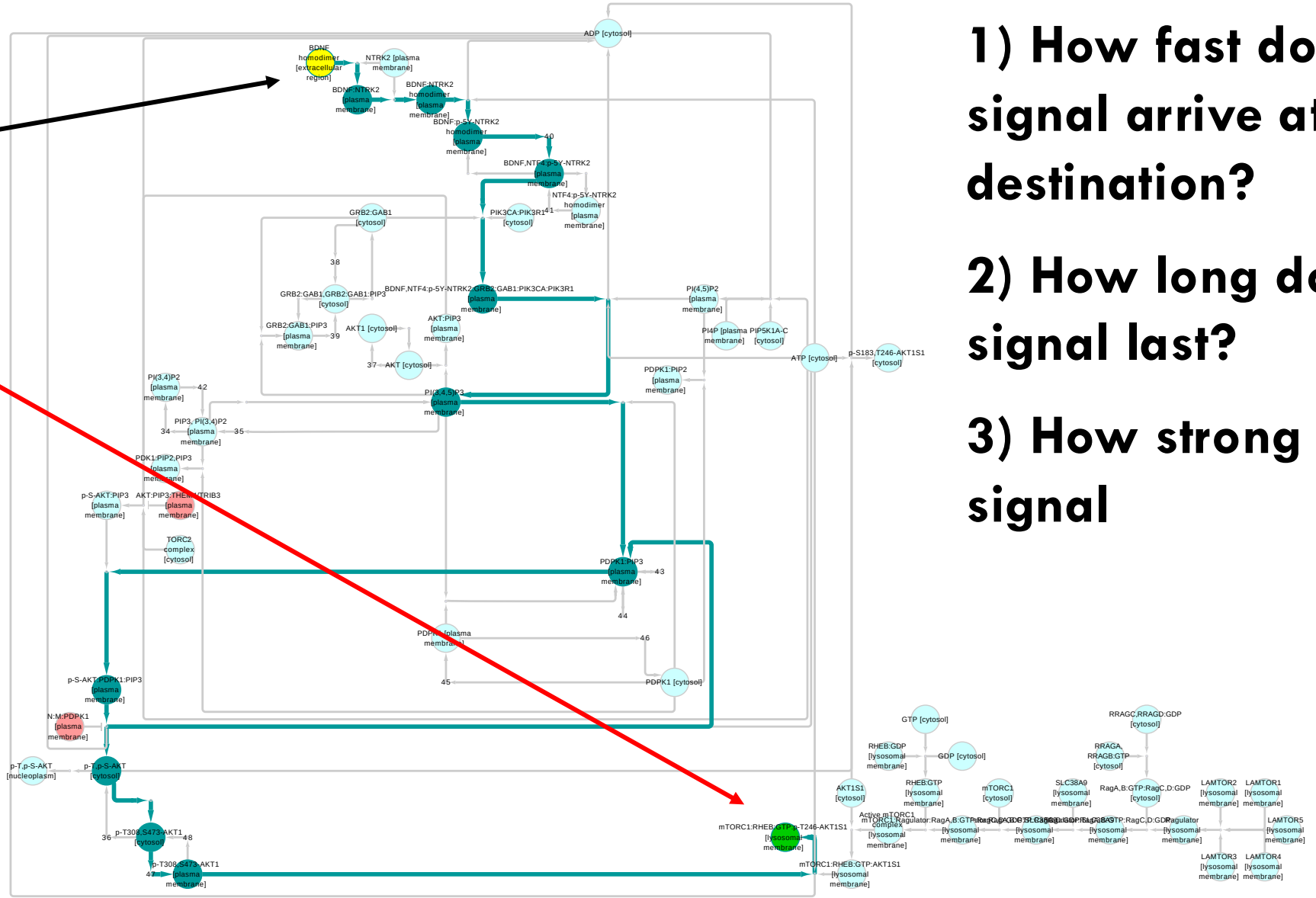
1) How fast does the signal arrive at its destination?

2) How long does the signal last?

Perspectives

Create dynamical signaling models





1) How fast does the signal arrive at its destination?

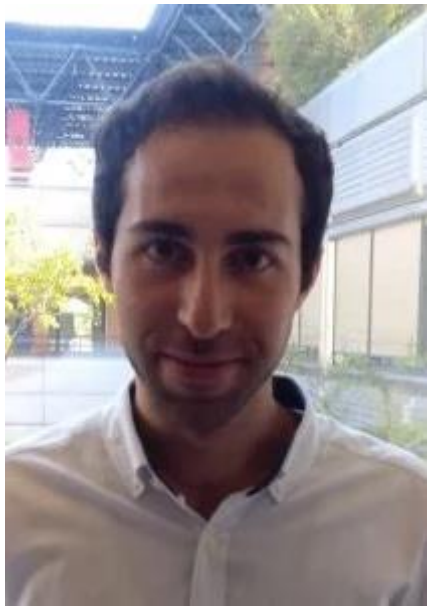
2) How long does the signal last?

3) How strong is the signal

Acknowledgements

Dr. Maria Masid

David Liaskos



Dr. Omid Oftadeh

Margherita Tonini

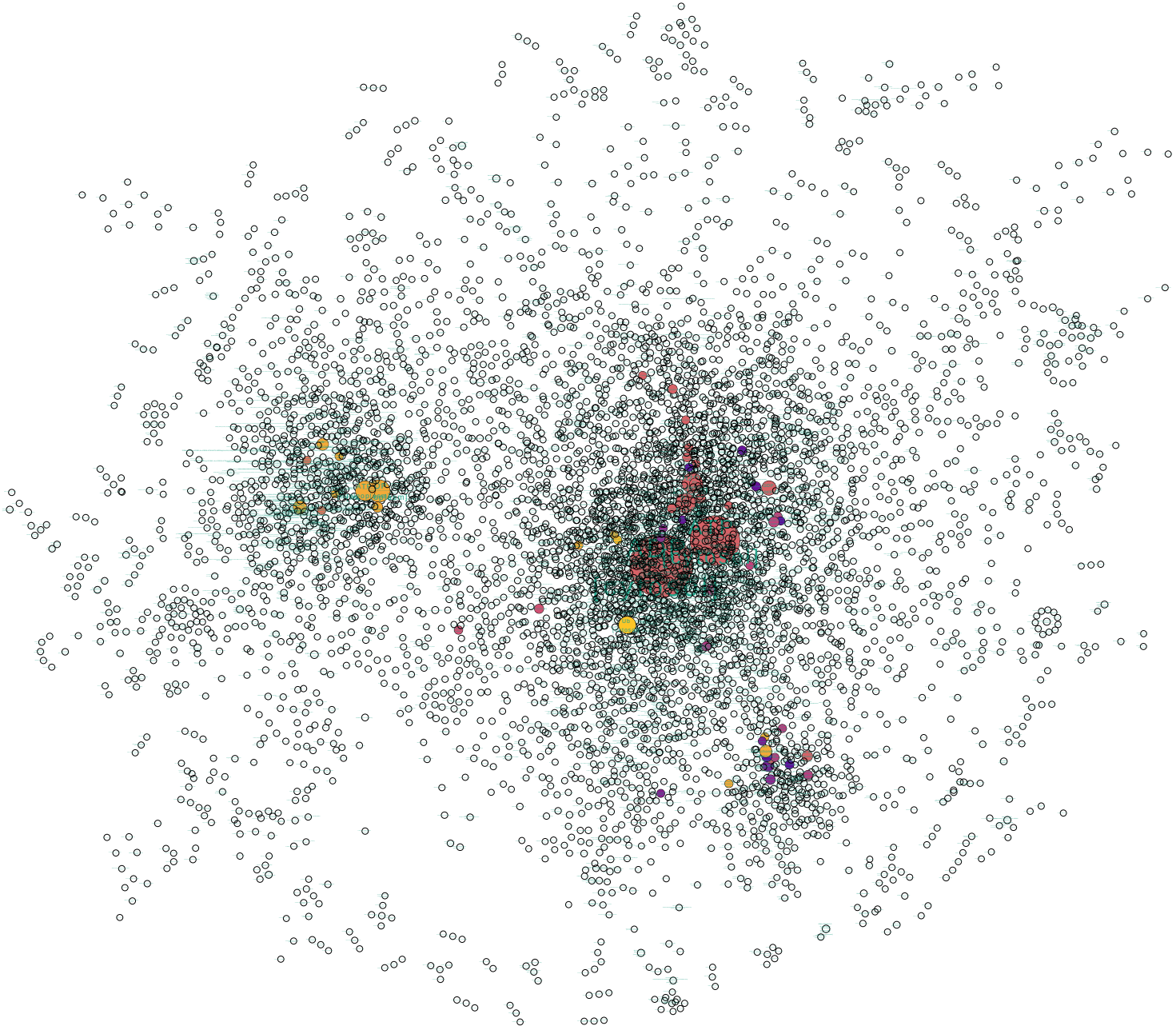
Roche

Nestlé

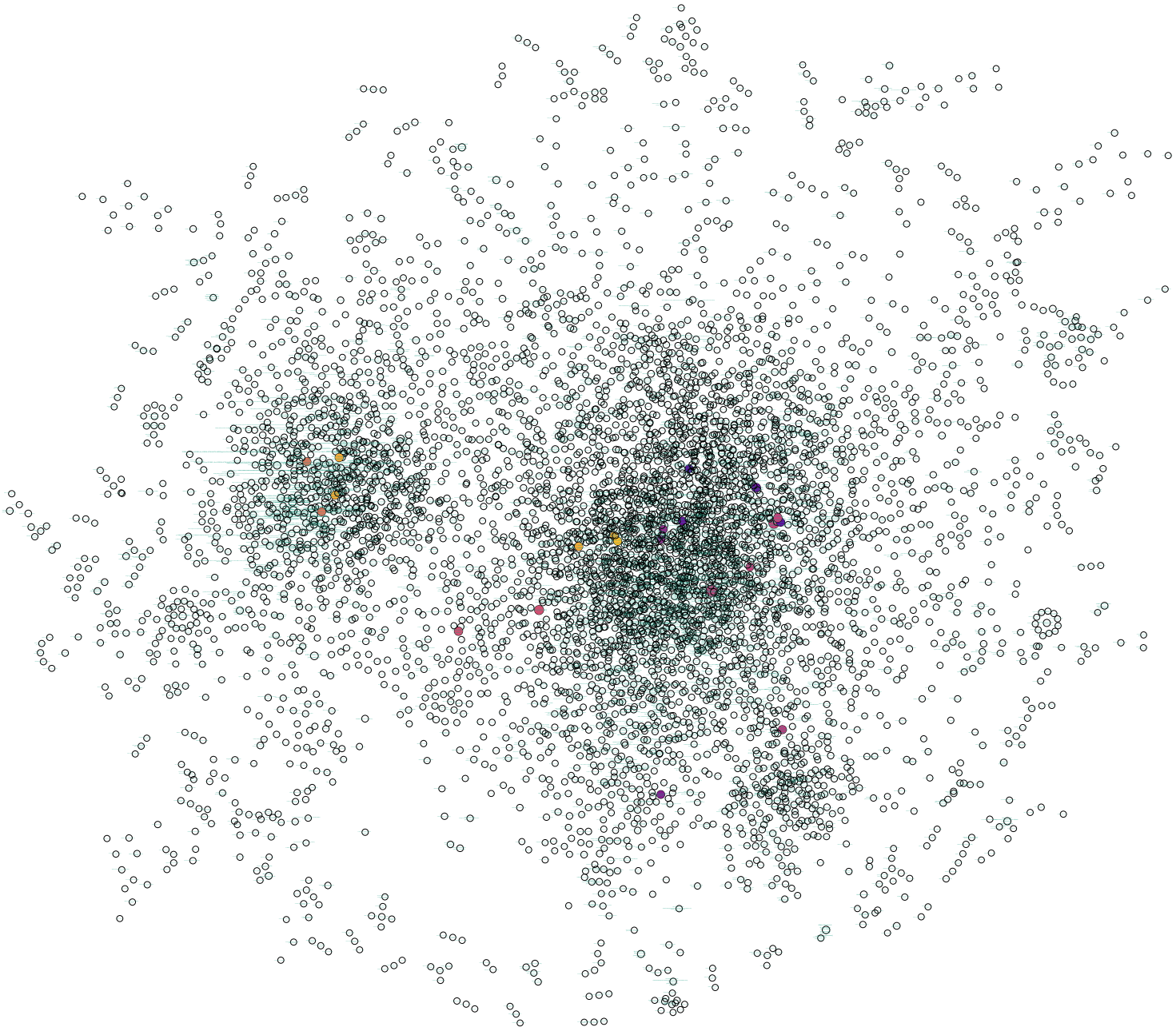
Swiss National Science Foundation

Questions

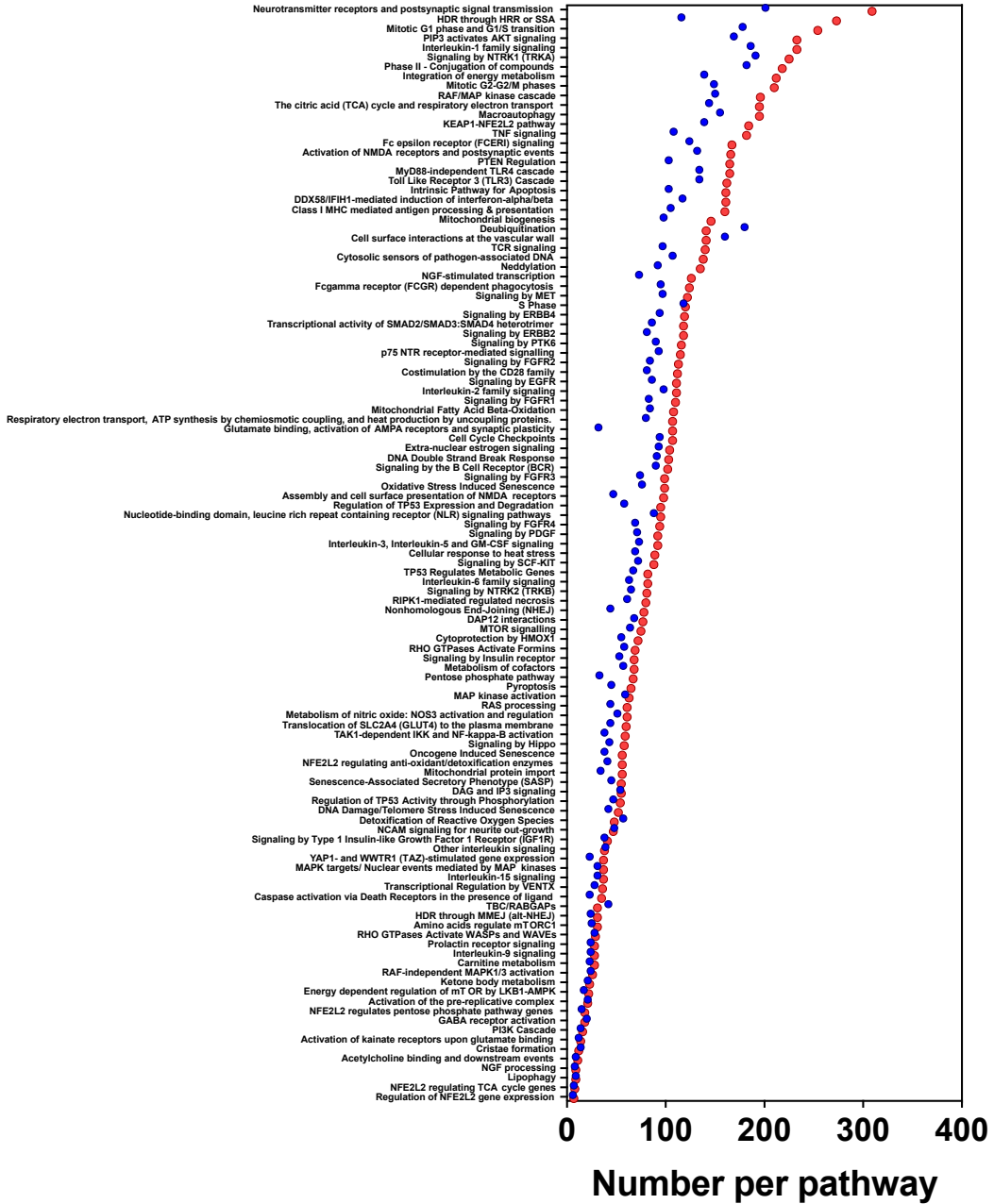
Co-factors identification and removal

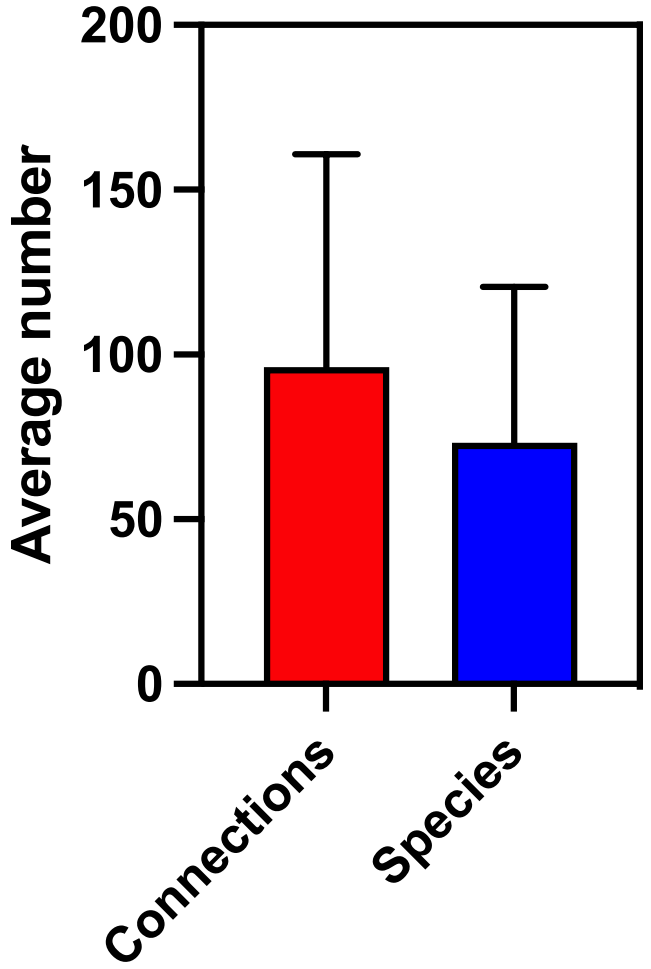


Co-factors identification and removal

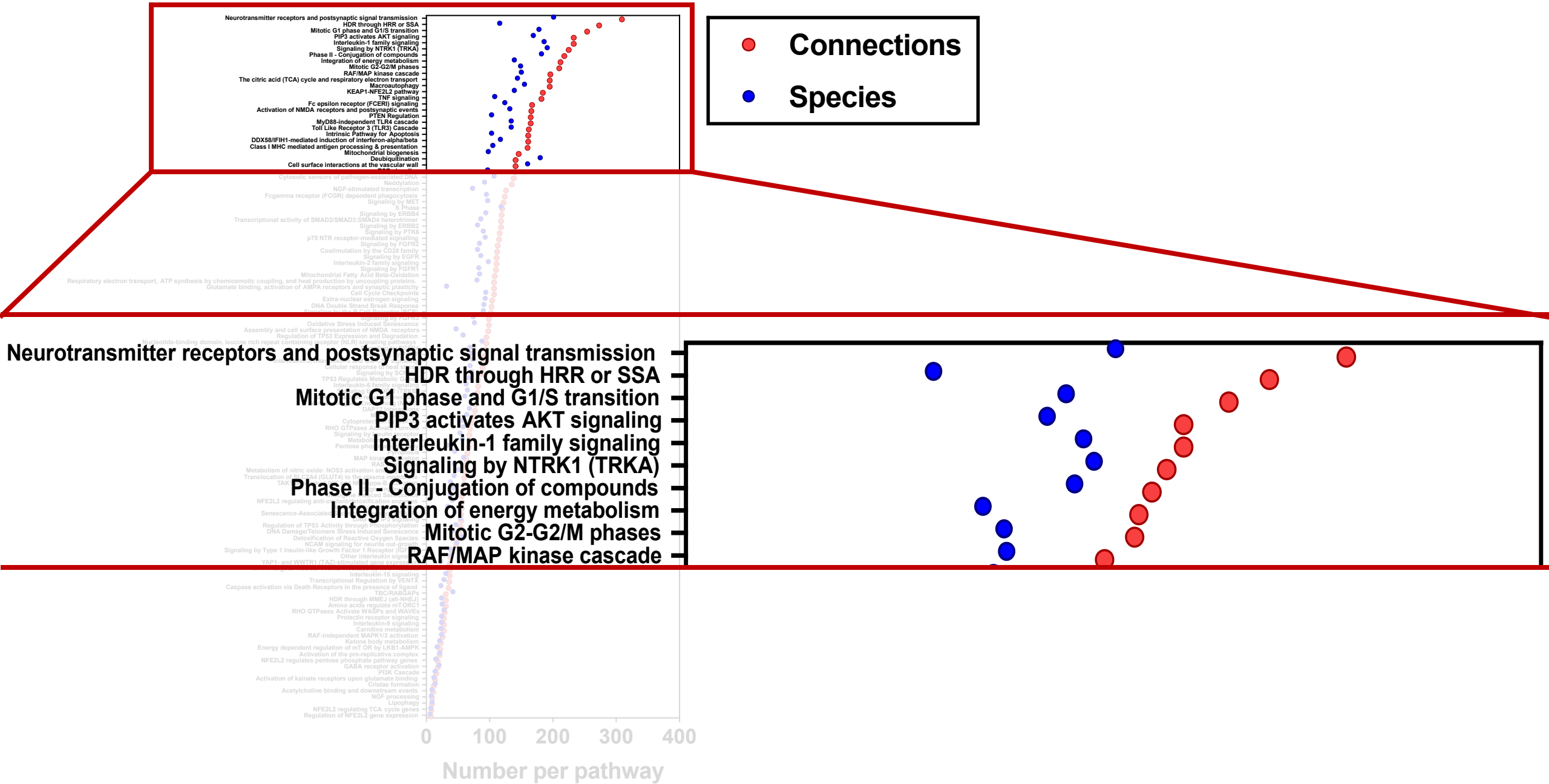


Analysis of the final network of selected pathways

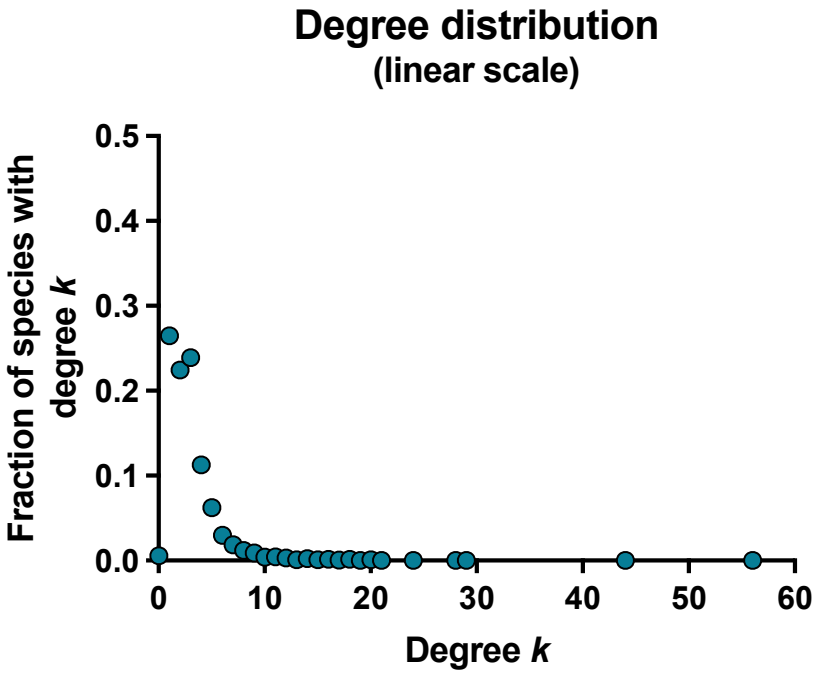


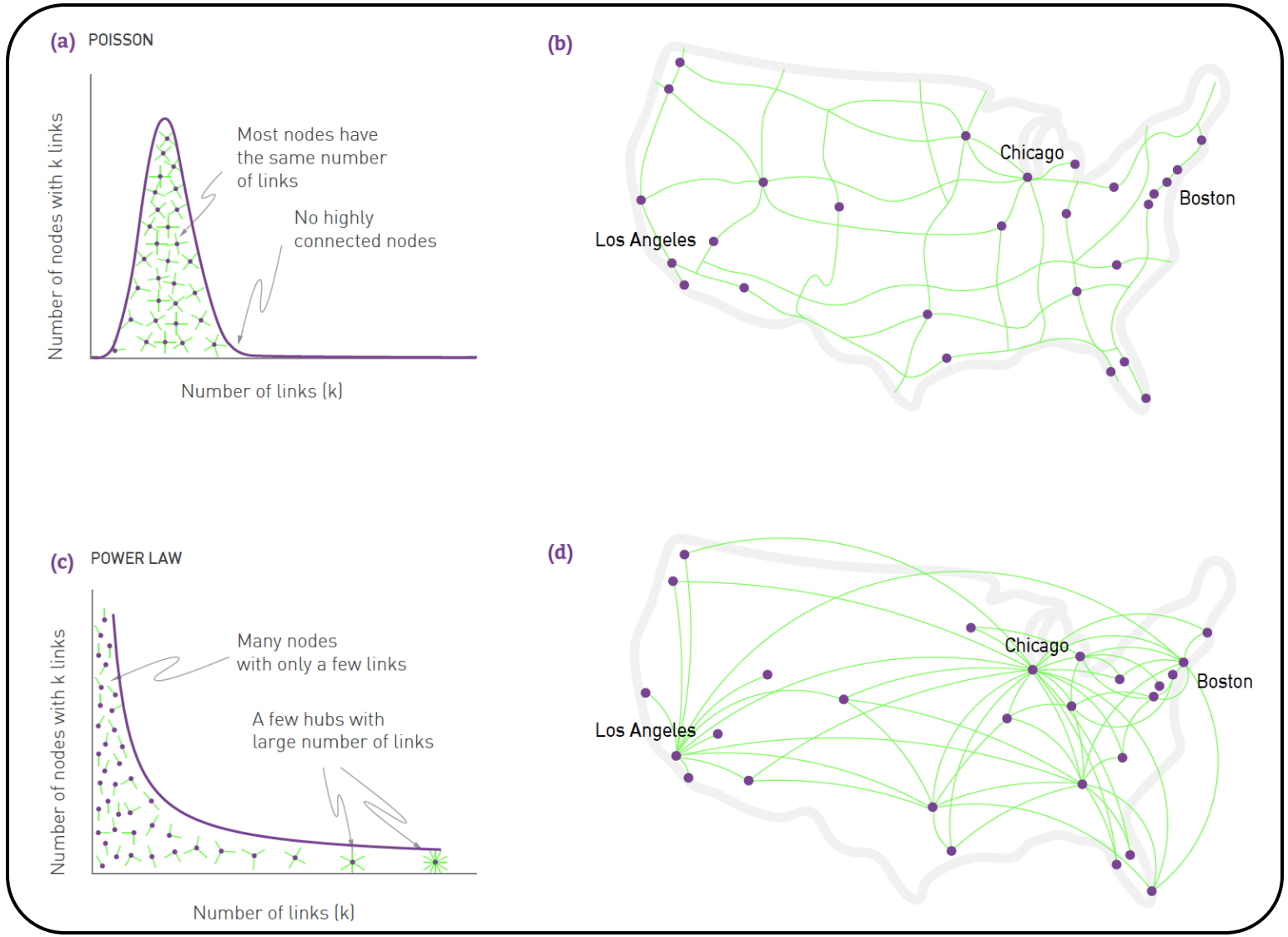


Analysis of the final network of selected pathways



Analysis of the final network of selected pathways



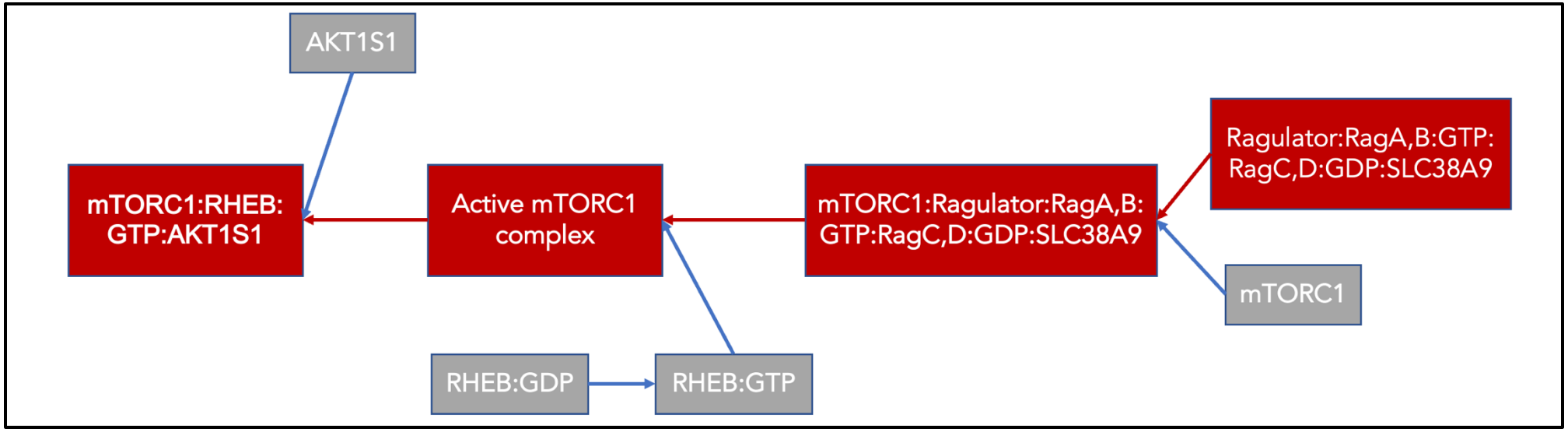


Erdos, Paul, and Renyi, Alfred. "On random graphs I", *Publ. Math. Debrecen,* 1959

Barabási, Albert-László, and Réka Albert. "Emergence of Scaling in Random Networks." *Science,* 1999

Barabási, Albert-László. *Network Science.* United Kingdom: Cambridge University Press, 2016

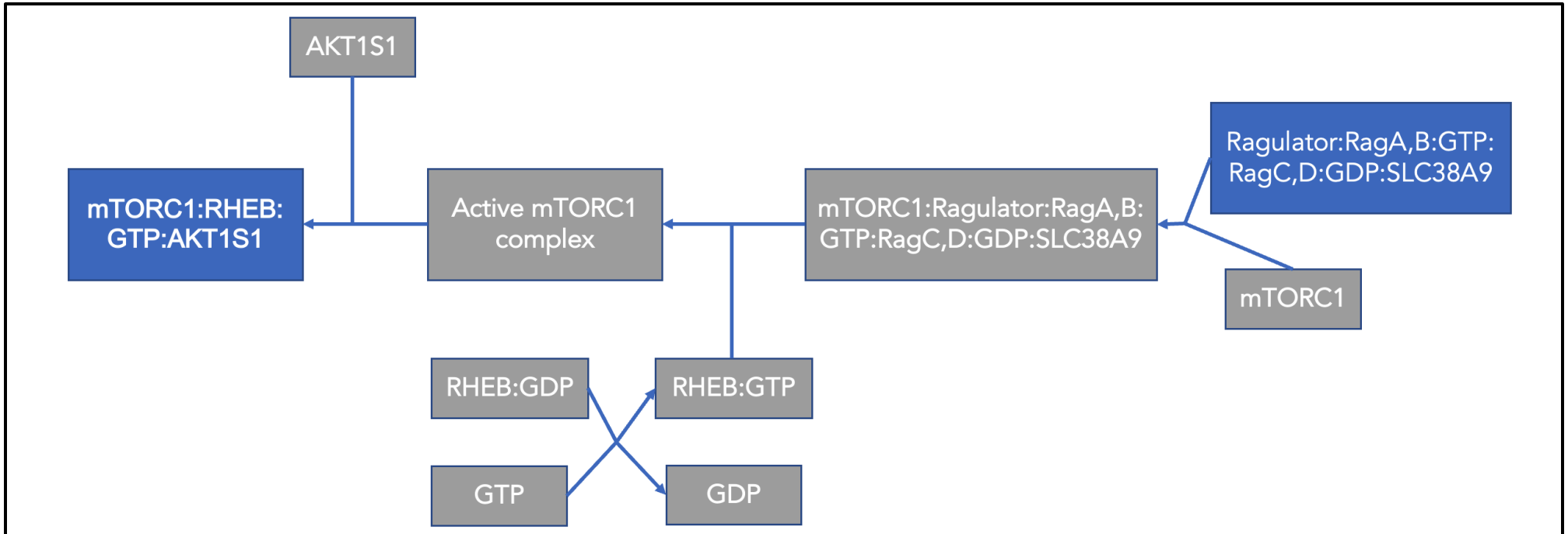
Method for generating balanced signaling networks



8 species
7 connections

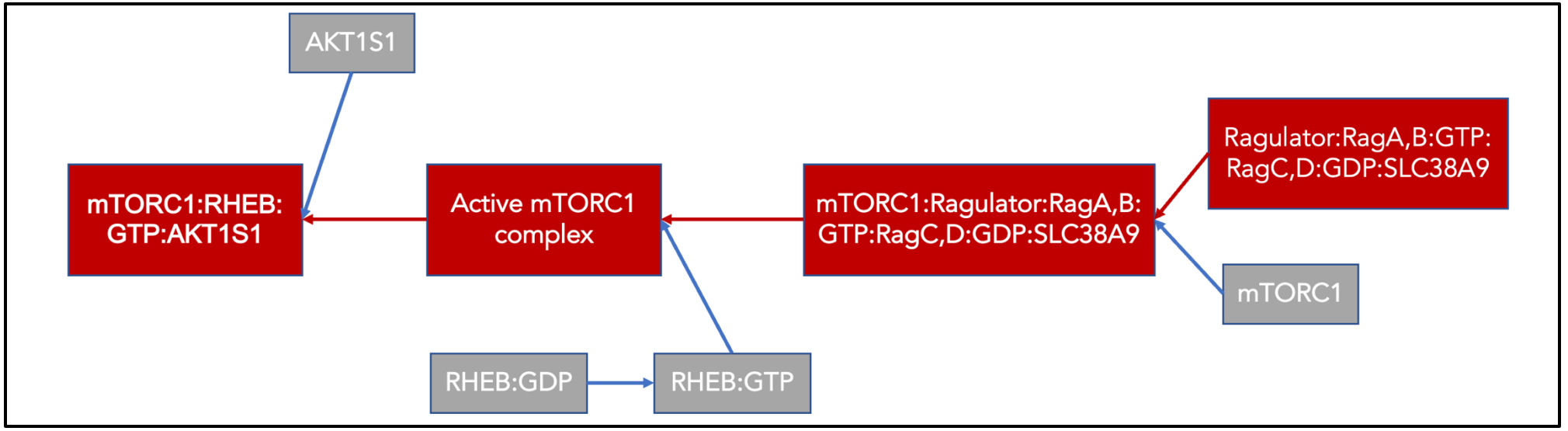
Minimal path

4 species
3 connections



10 species
4 reactions

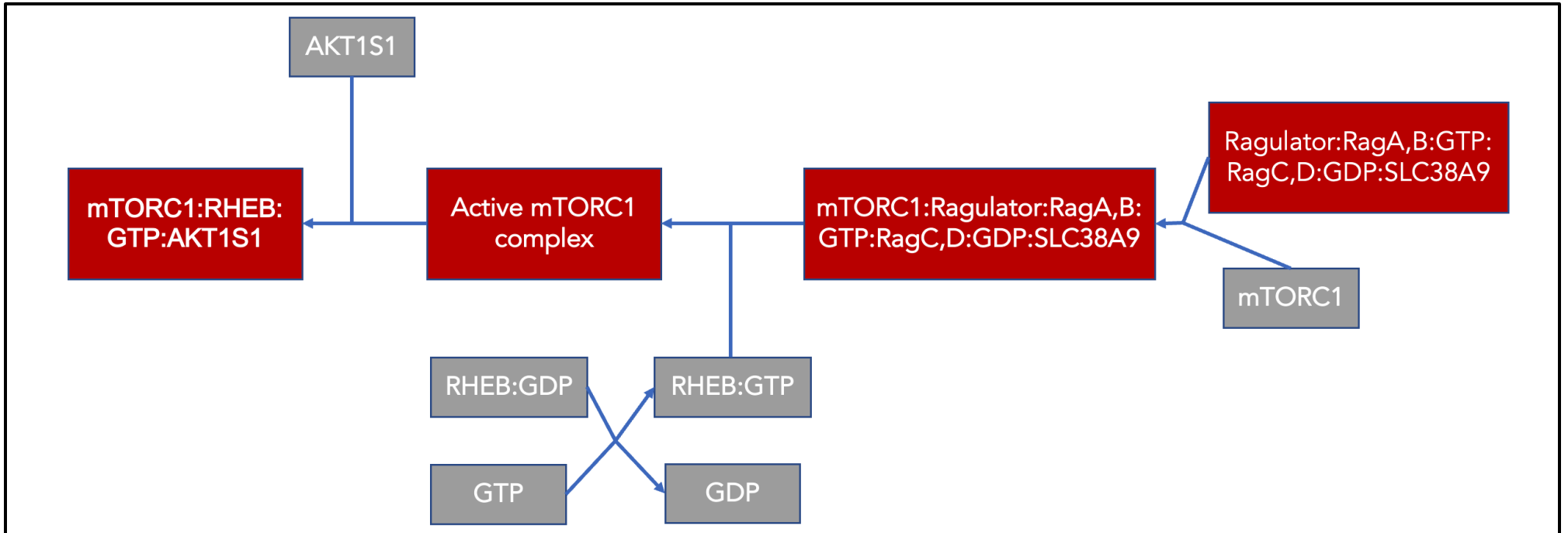
Method for generating balanced signaling networks



8 species
7 connections

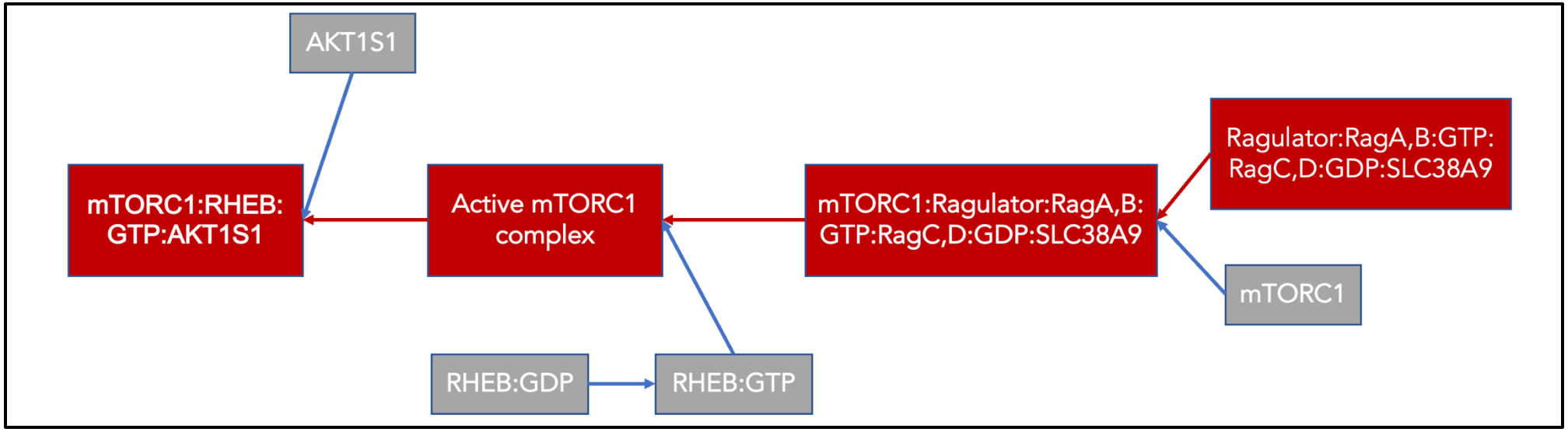
Minimal path

4 species
3 connections



10 species
4 reactions

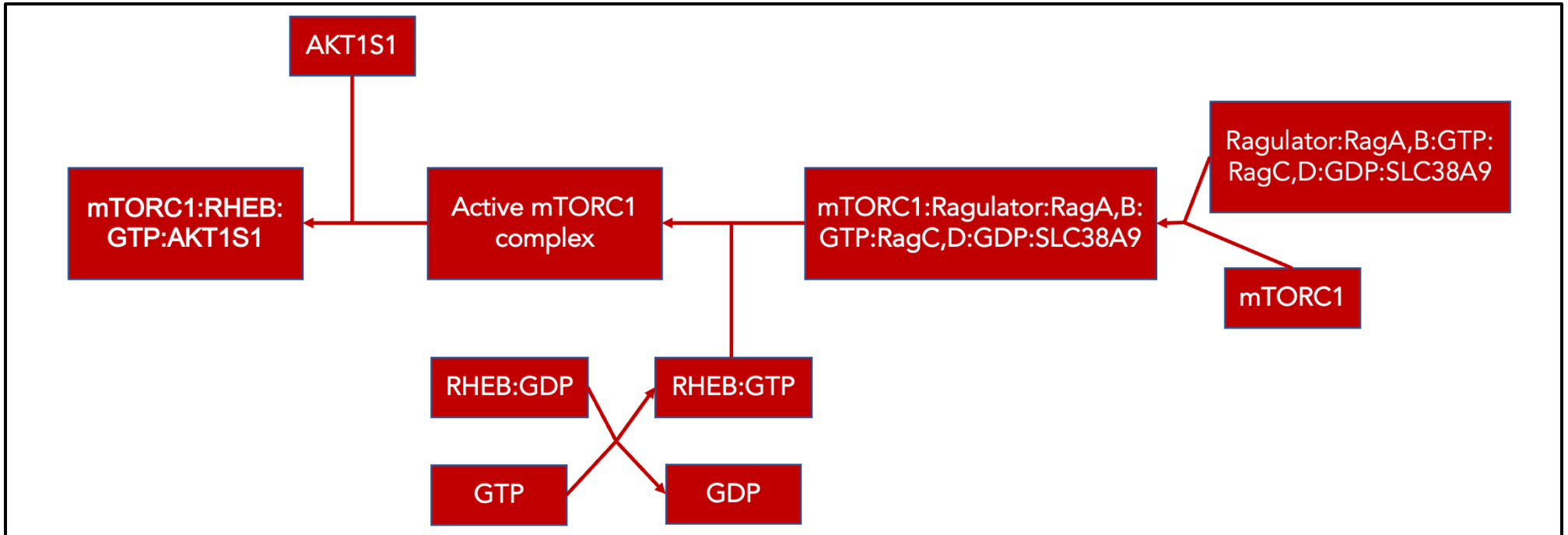
Method for generating balanced signaling networks



8 species
7 connections

Minimal path

4 species
3 connections

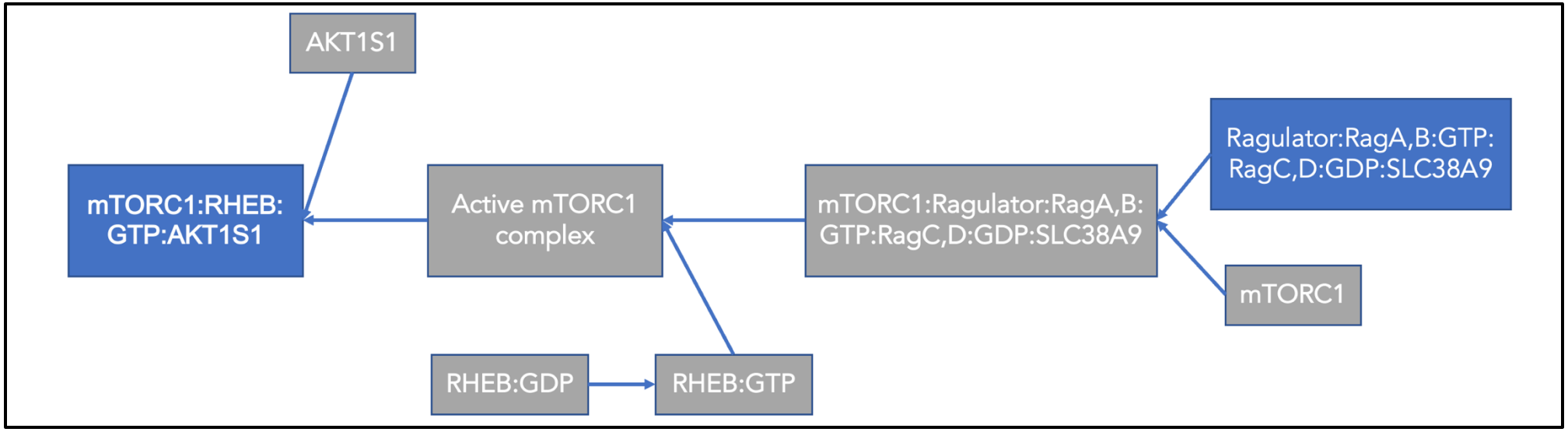


10 species
4 reactions

Balanced path

10 species
4 reactions

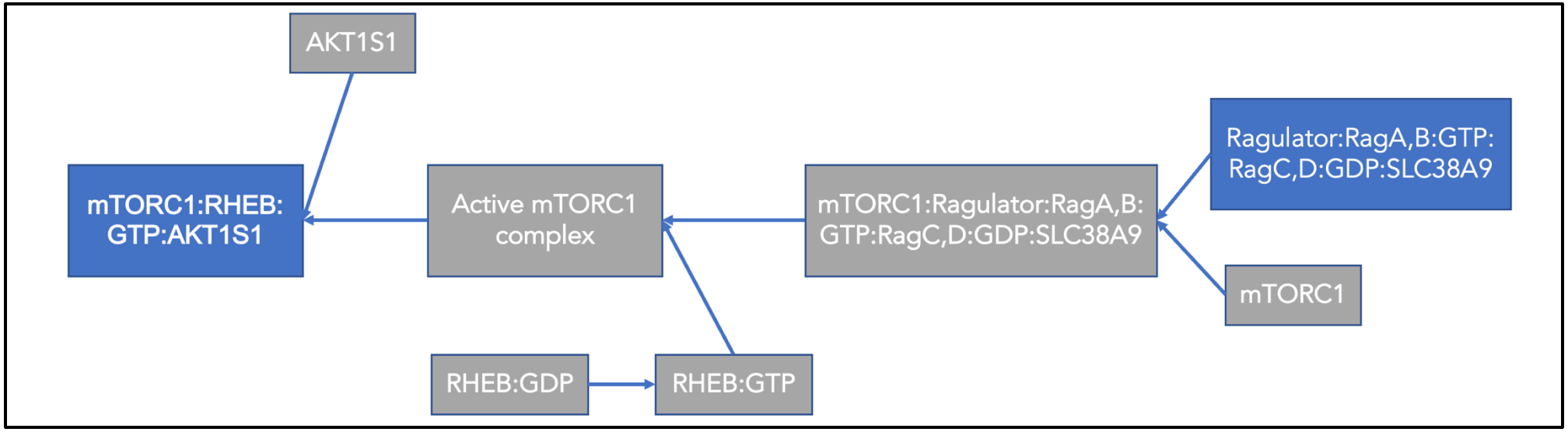
Method for generating balanced signaling networks



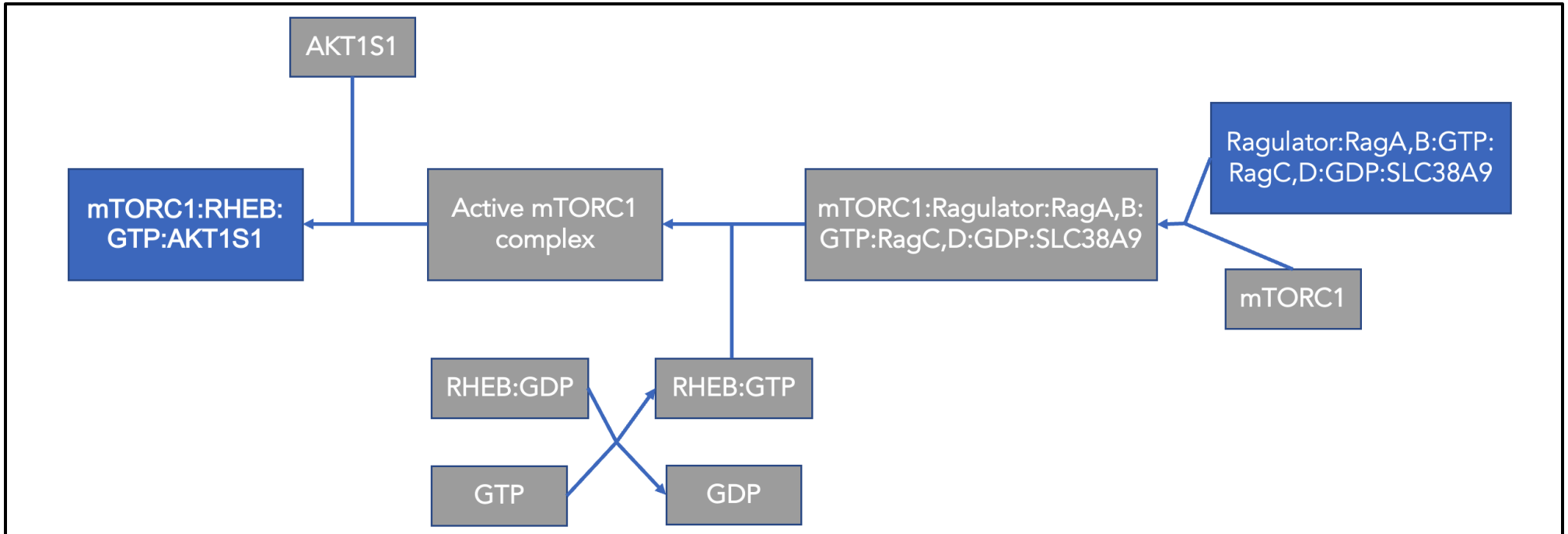
8 species

7 connections

Method for generating balanced signaling networks



8 species
7 connections

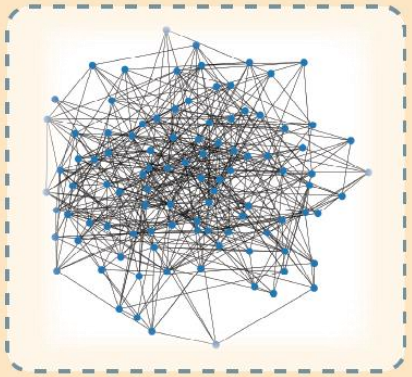


10 species
4 reactions

Add co-factors back to balance our network.

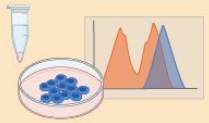
Study deregulation in signaling pathways

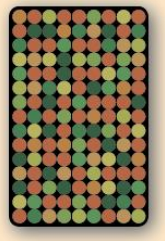
SIGMA Method



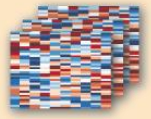
Signaling network

omics data

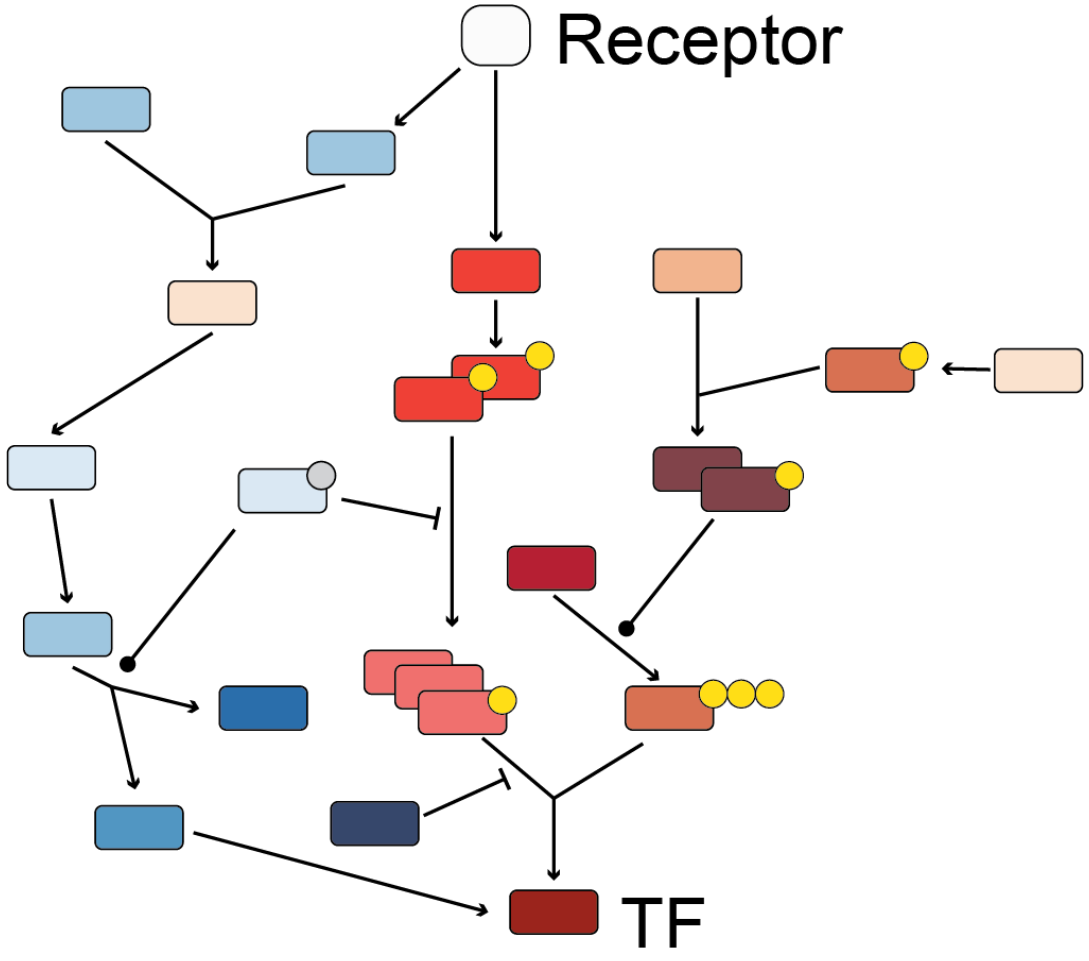




phosphoproteomics

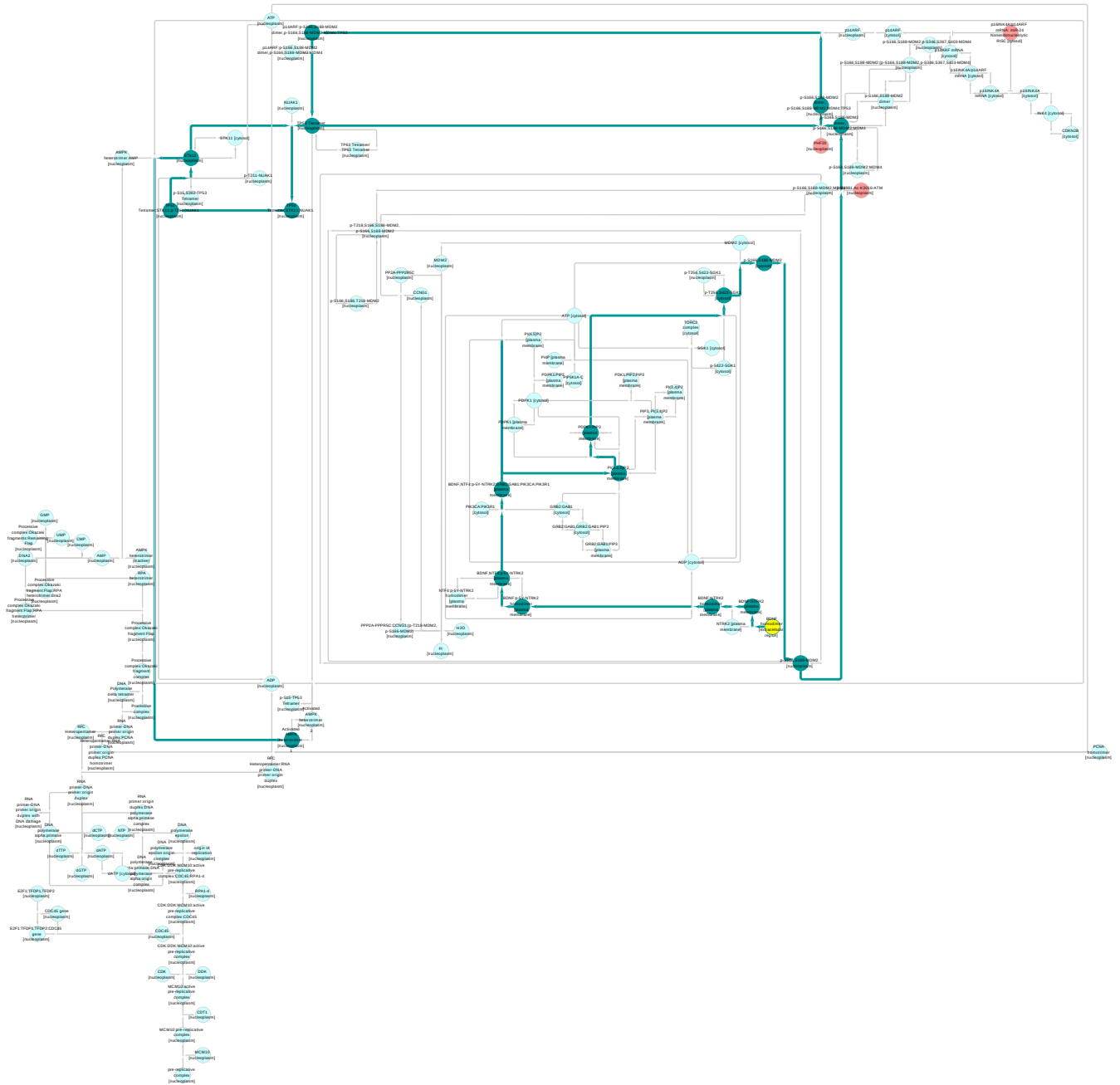


(sc)RNA-seq data

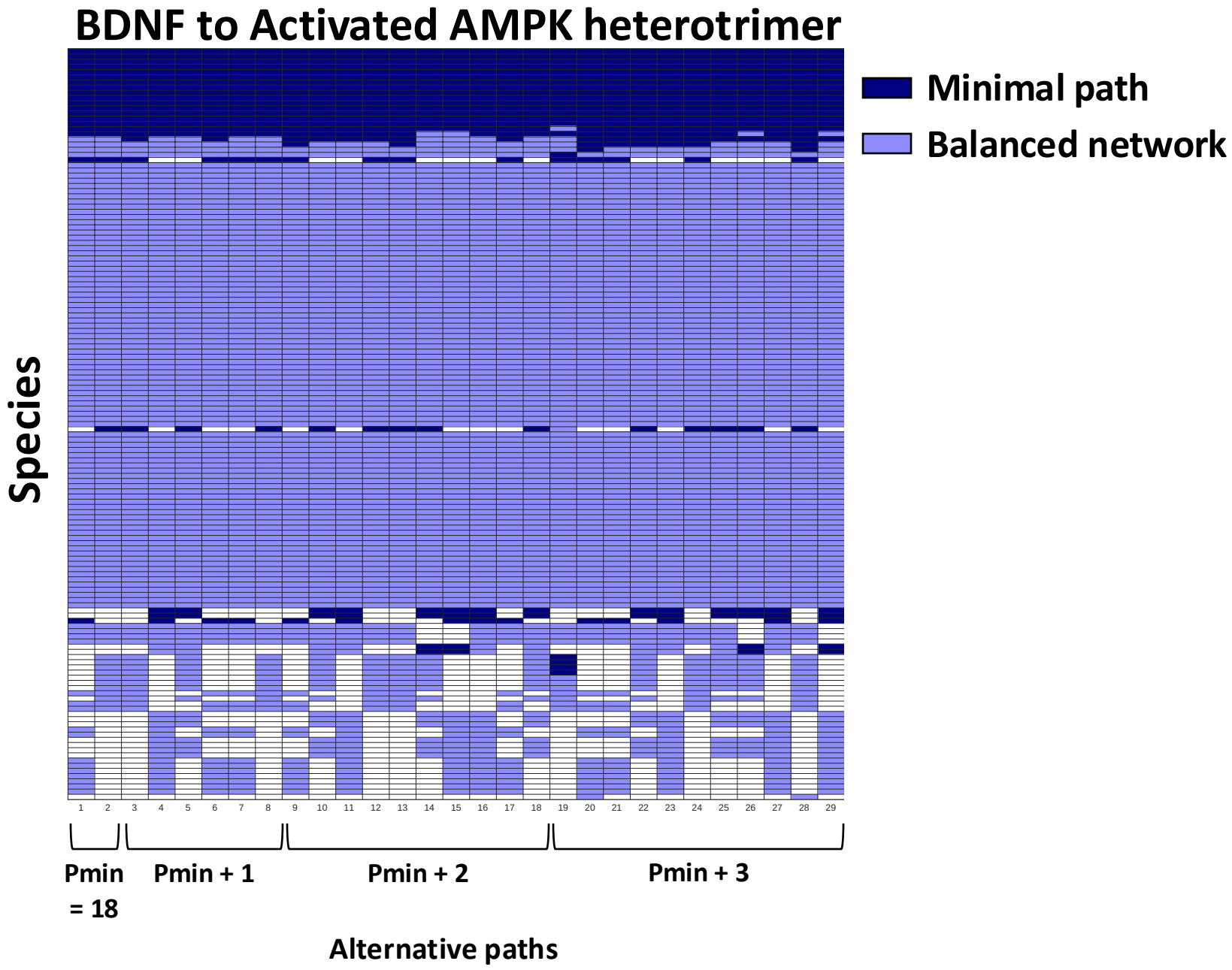


enrichment analysis

Studying BDNF connection to AMPK

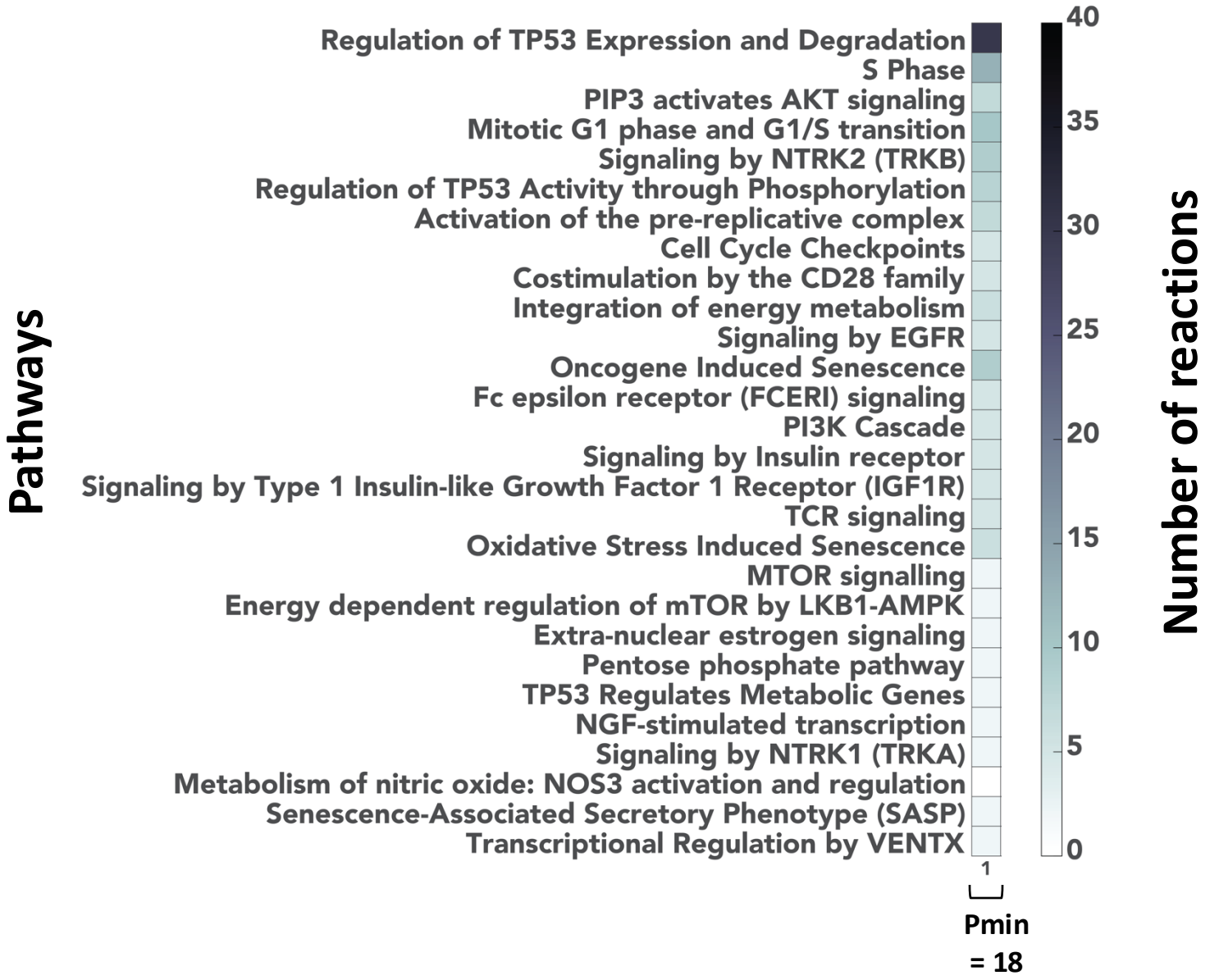


Studying BDNF connection to AMPK



Studying BDNF connection to AMPK

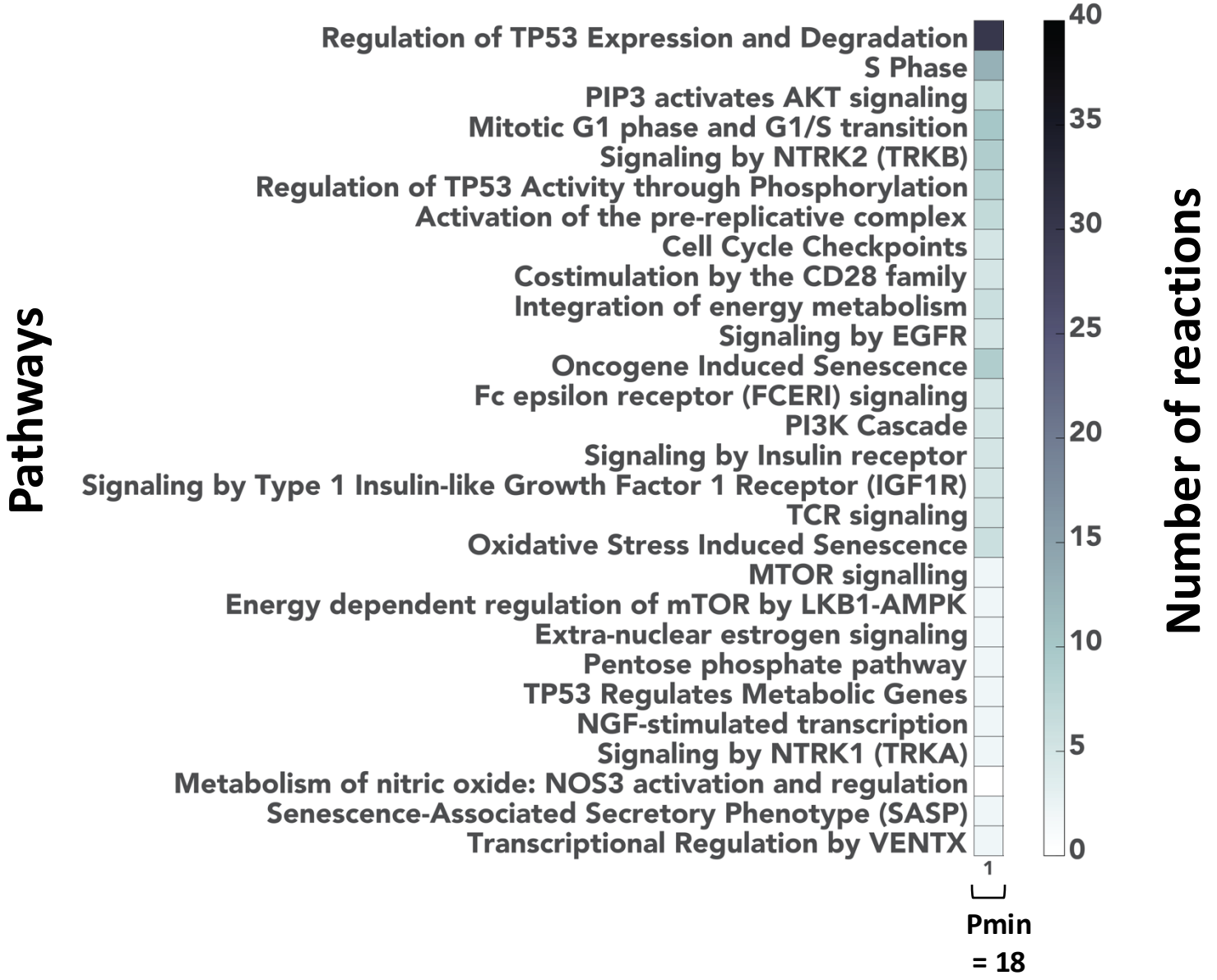
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK

Studying BDNF connection to AMPK

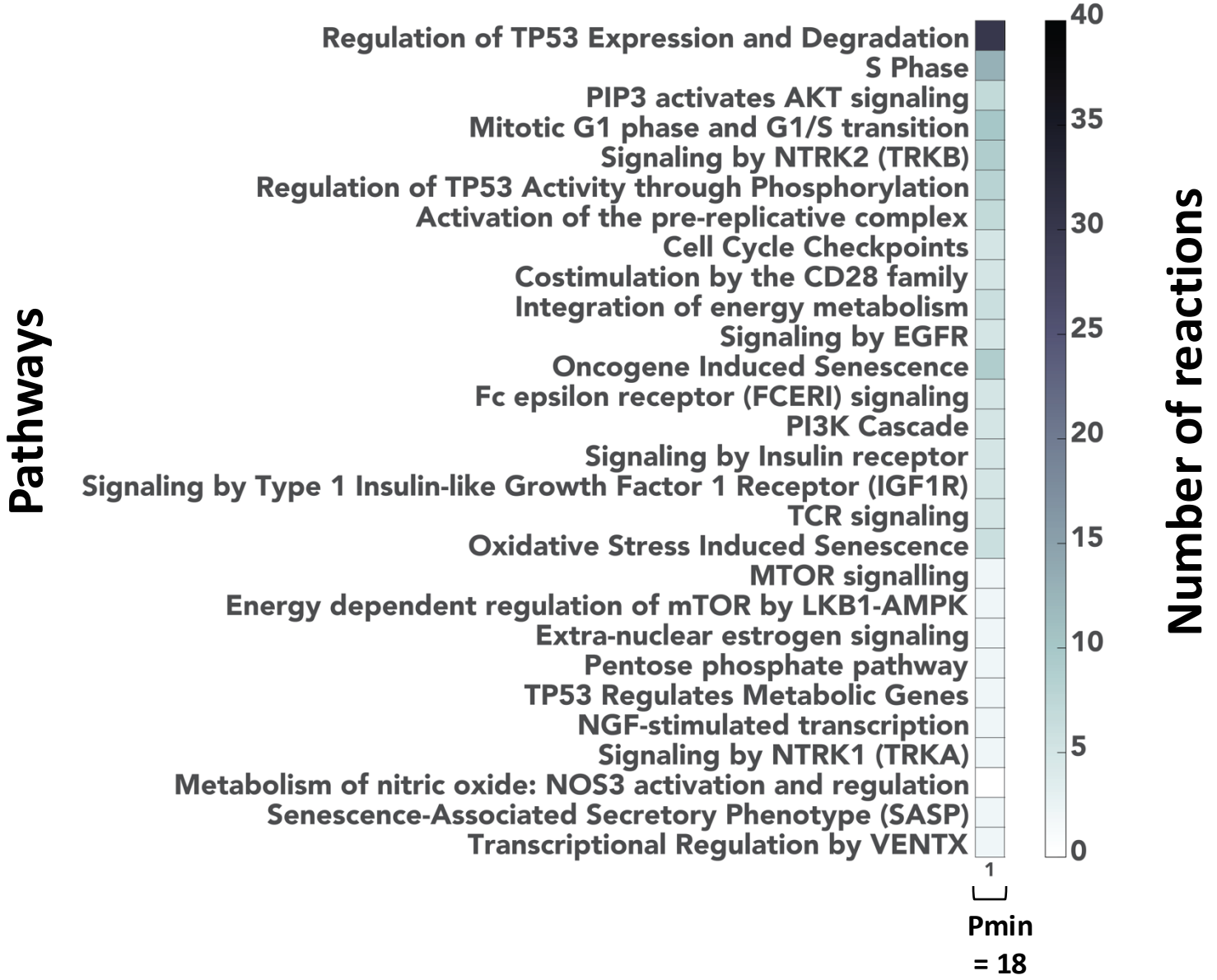
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK
- Total of 104 reactions (including the peripheral)

Studying BDNF connection to AMPK

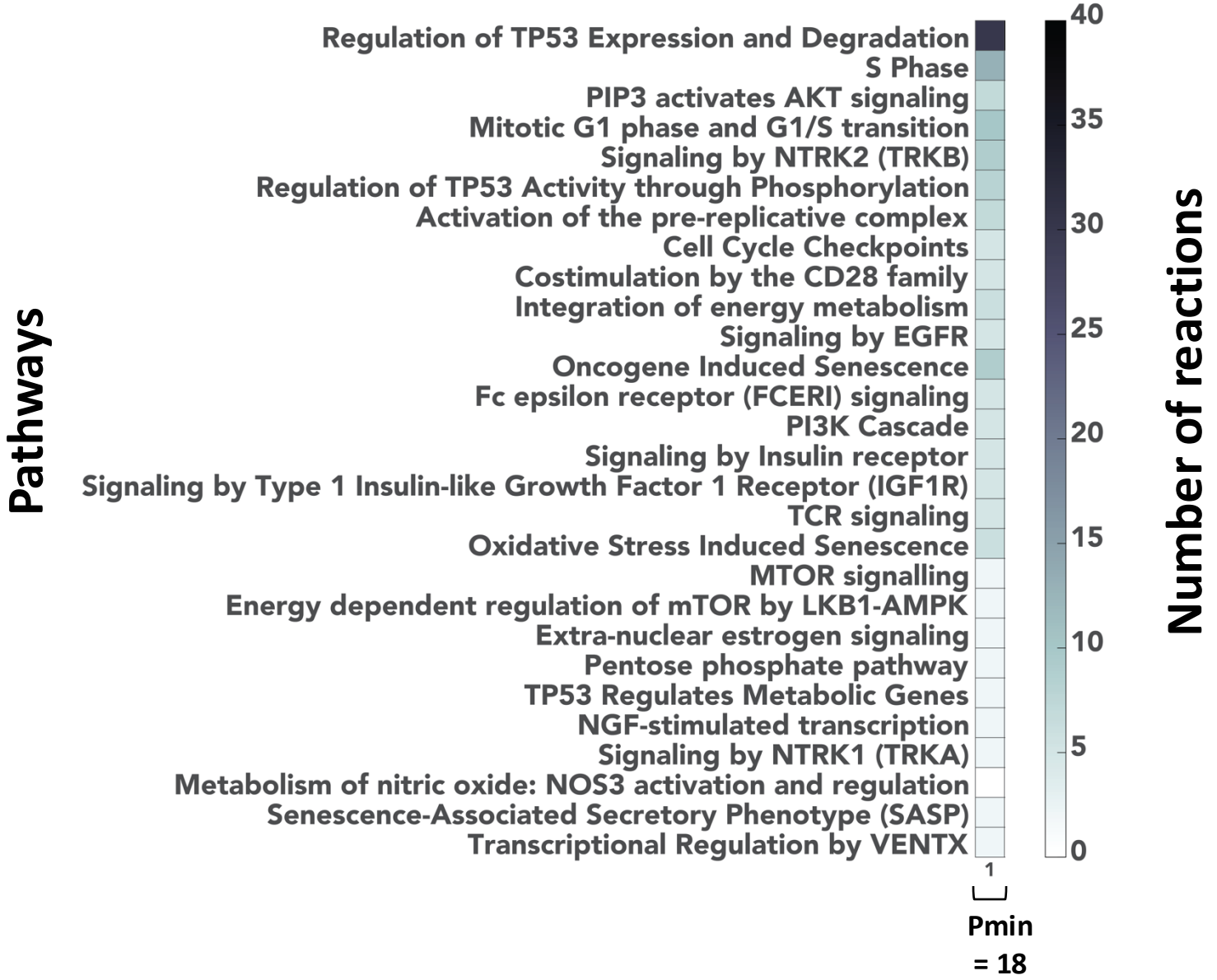
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK
- Total of 104 reactions (including the peripheral)
- These 104 reactions from 27 pathways

Studying BDNF connection to AMPK

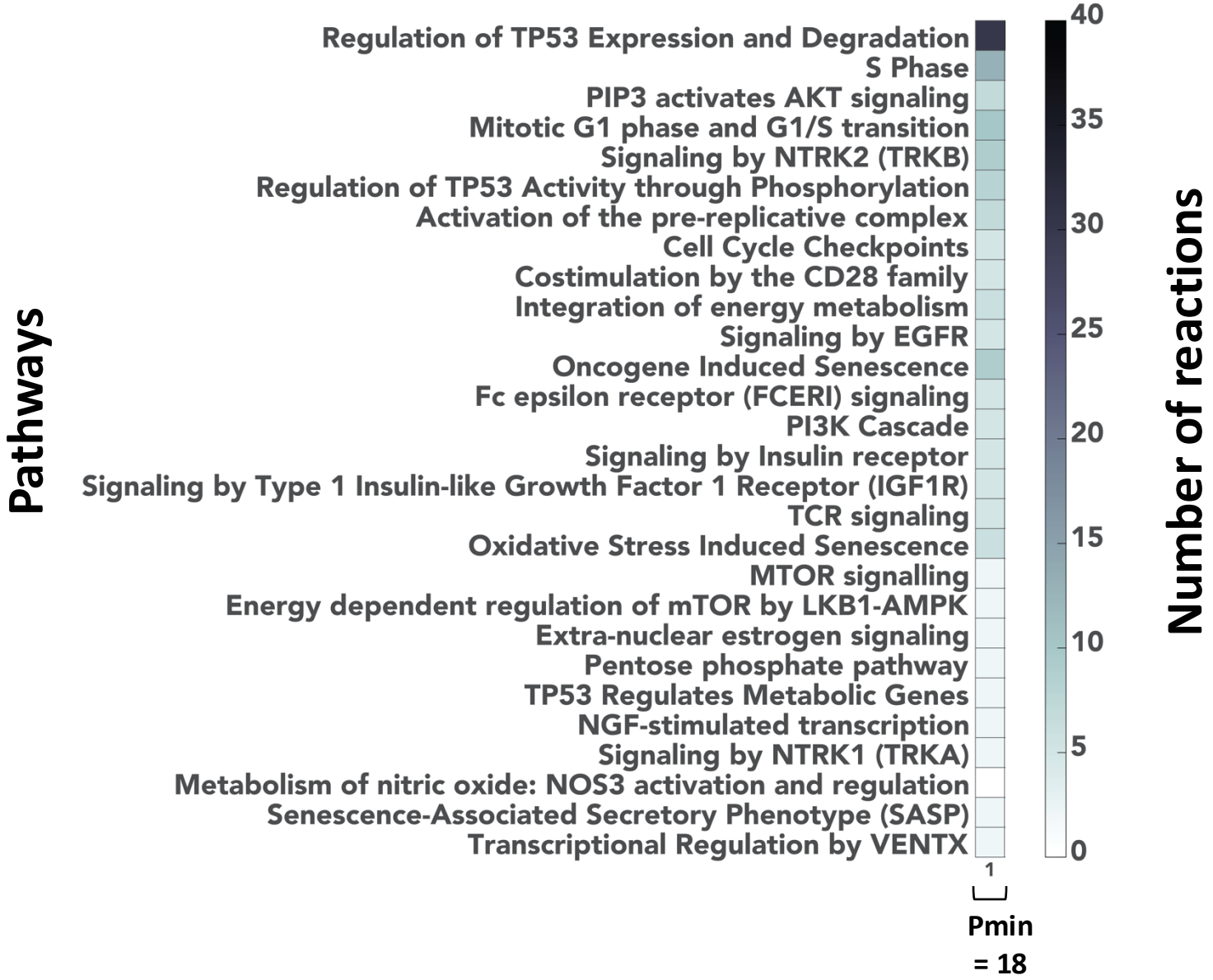
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK
- Total of 104 reactions (including the peripheral)
- These 104 reactions from 27 pathways
- Max of 30 reactions in Regulation of TP53

Studying BDNF connection to AMPK

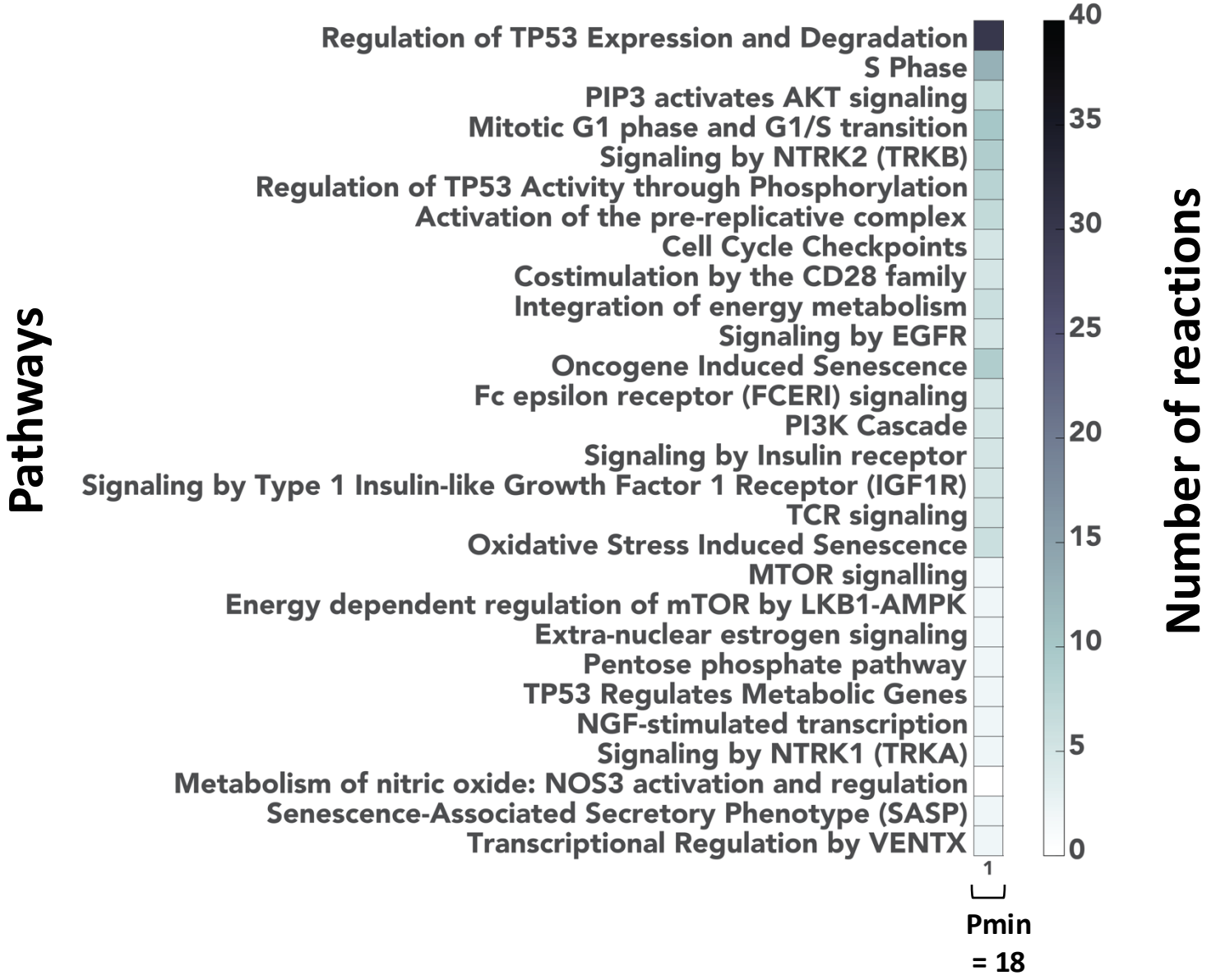
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK
- Total of 104 reactions (including the peripheral)
- These 104 reactions from 27 pathways
- Max of 30 reactions in Regulation of TP53
- Min of 2 reactions in 9 pathways

Studying BDNF connection to AMPK

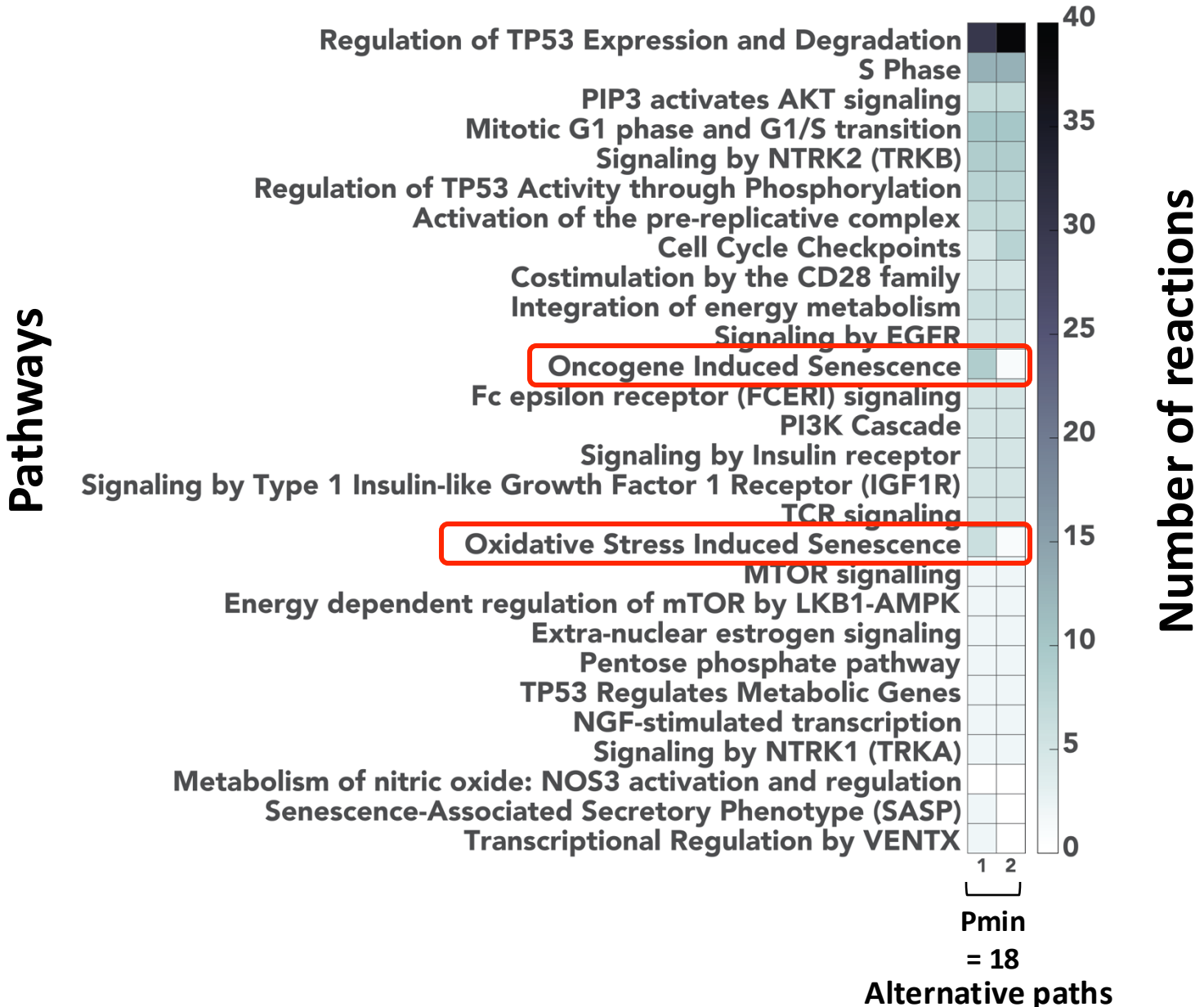
BDNF to Activated AMPK heterotrimer



- 18 steps from BDNF to AMPK
- Total of 104 reactions (including the peripheral)
- These 104 reactions from 27 pathways
- Max of 30 reactions in Regulation of TP53
- Min of 2 reactions in 9 pathways
- Metabolism of nitric oxide does not participate in this path

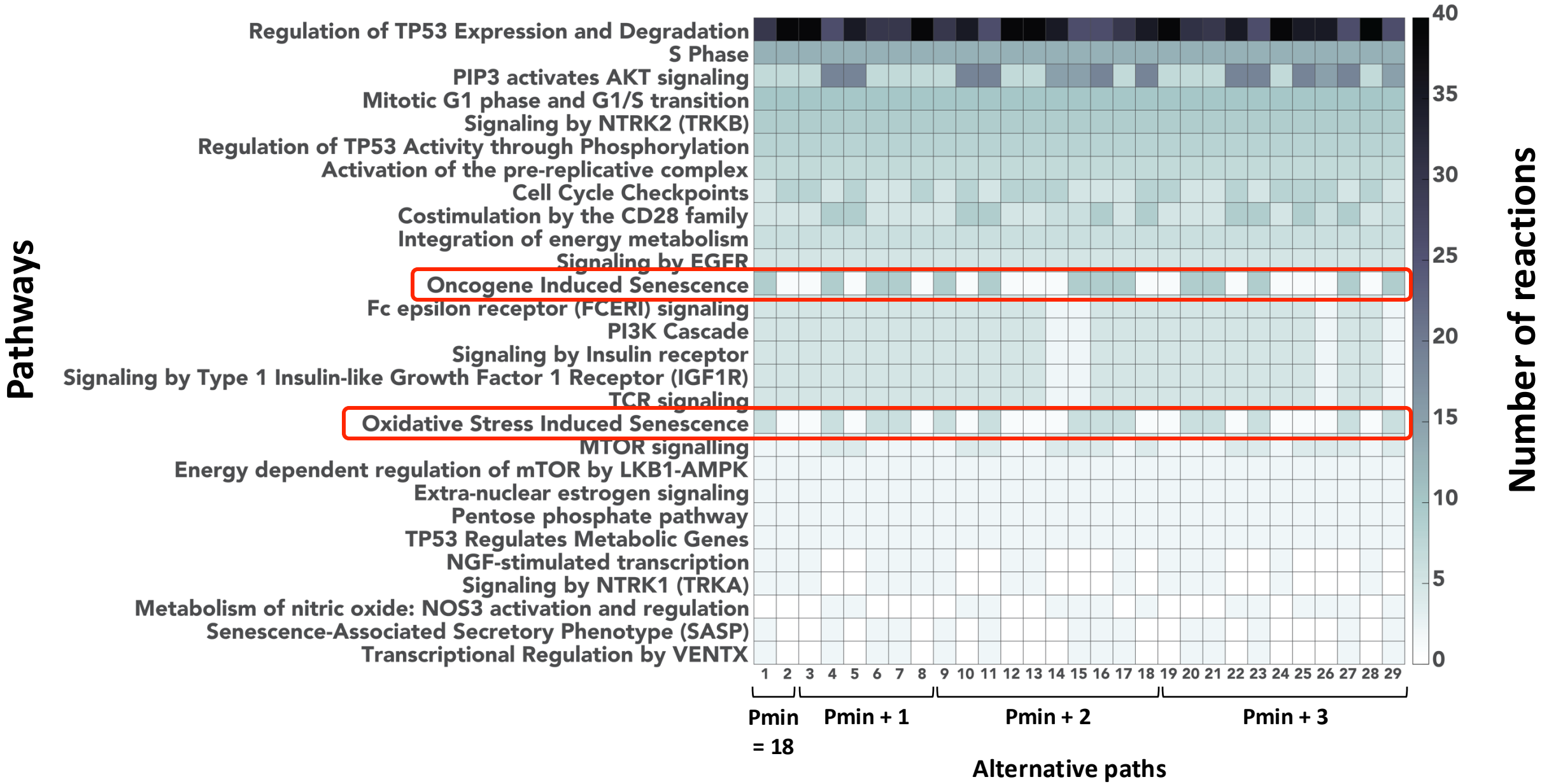
Studying BDNF connection to AMPK

BDNF to Activated AMPK heterotrimer

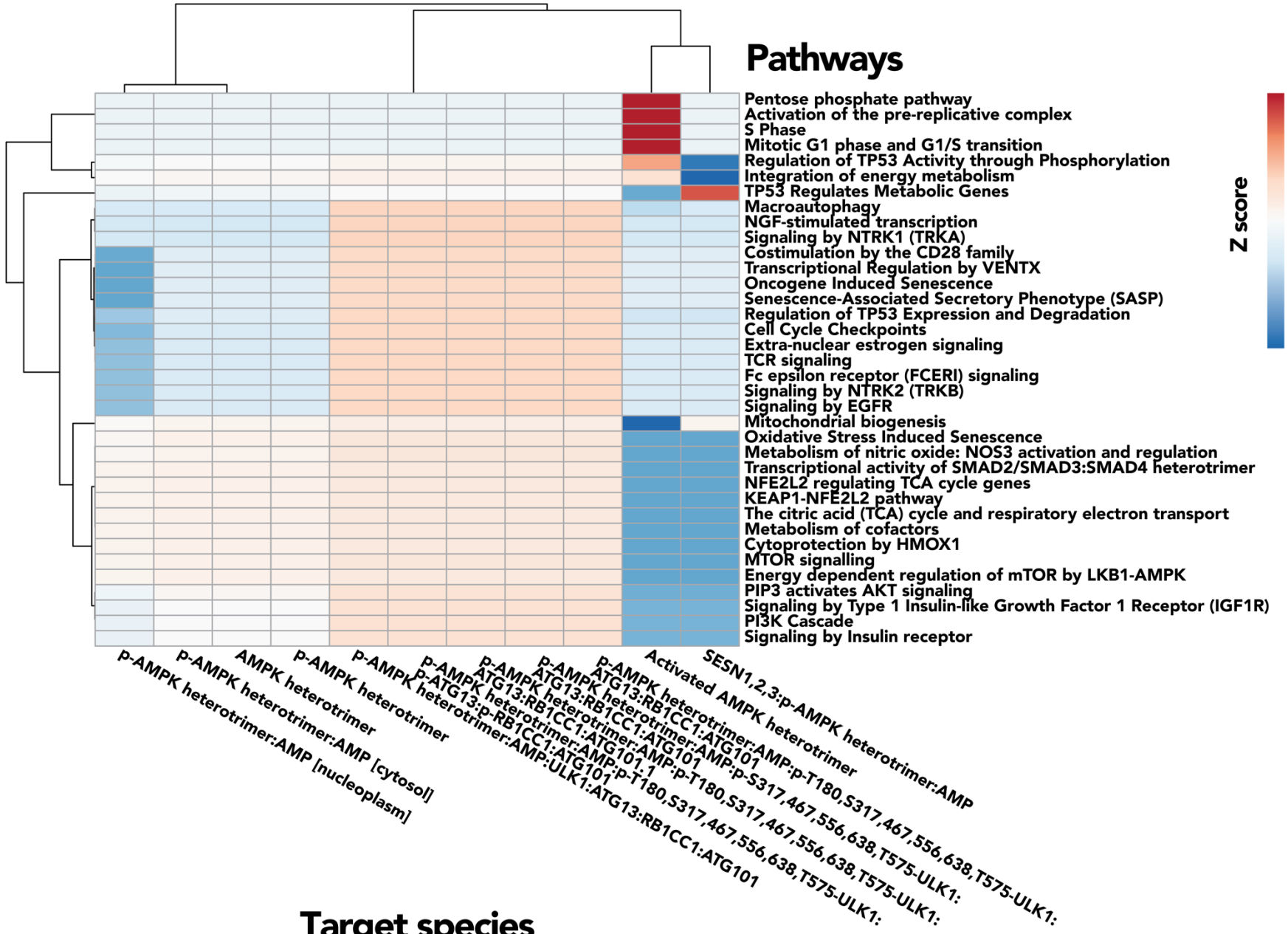


Studying BDNF connection to AMPK

BDNF to Activated AMPK heterotrimer



Studying BDNF connection to AMPK



Studying BDNF connection to AMPK