Genome-scale metabolic models (GEMs) of human and model animals - a platform for translational research

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GOTBIN seminar
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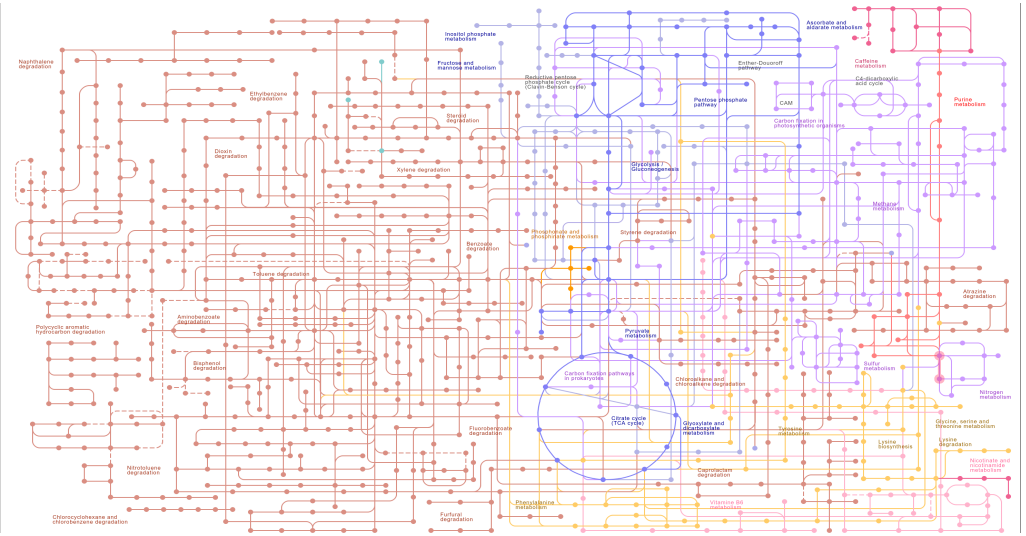
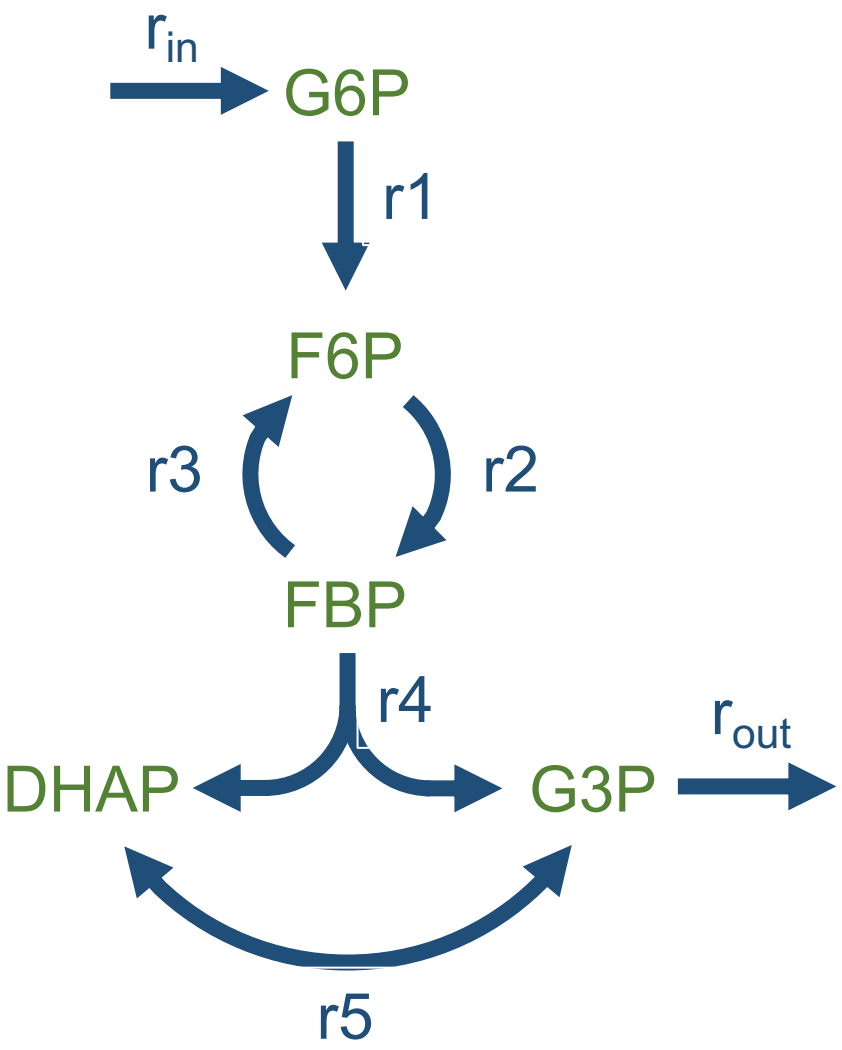


Content

- What is a genome-scale metabolic models (GEM)
- Human-GEM generation and curation
- Animal GEMs
- GEM applications
- Metabolic Atlas
- A coherent and evolving platform for translational medicine

The Stoichiometric matrix in GEM



Reactions

Metabolites

	r1	r2	r3	r4	r5
G6P	**−1**	0	0	0	0
F6P	**1**	**−1**	**1**	0	0
FBP	0	**1**	**−1**	**−1**	0
DHAP	0	0	0	**1**	**−1**
G3P	0	0	0	**1**	**1**

S

Components in a GEM

Transcript IDs

GO Terms

Orthologs

…

Chemical formula
Charge
InChI code
Other IDs
…

Proteins (UniProt ID)

P06744

P09467, O00757

P04075, P05062, P09972

P60174

Genes (symbol)

GPI

n/a

FBP1, FBP2

ALDOA, ALDOB, ALDOC

TPI1

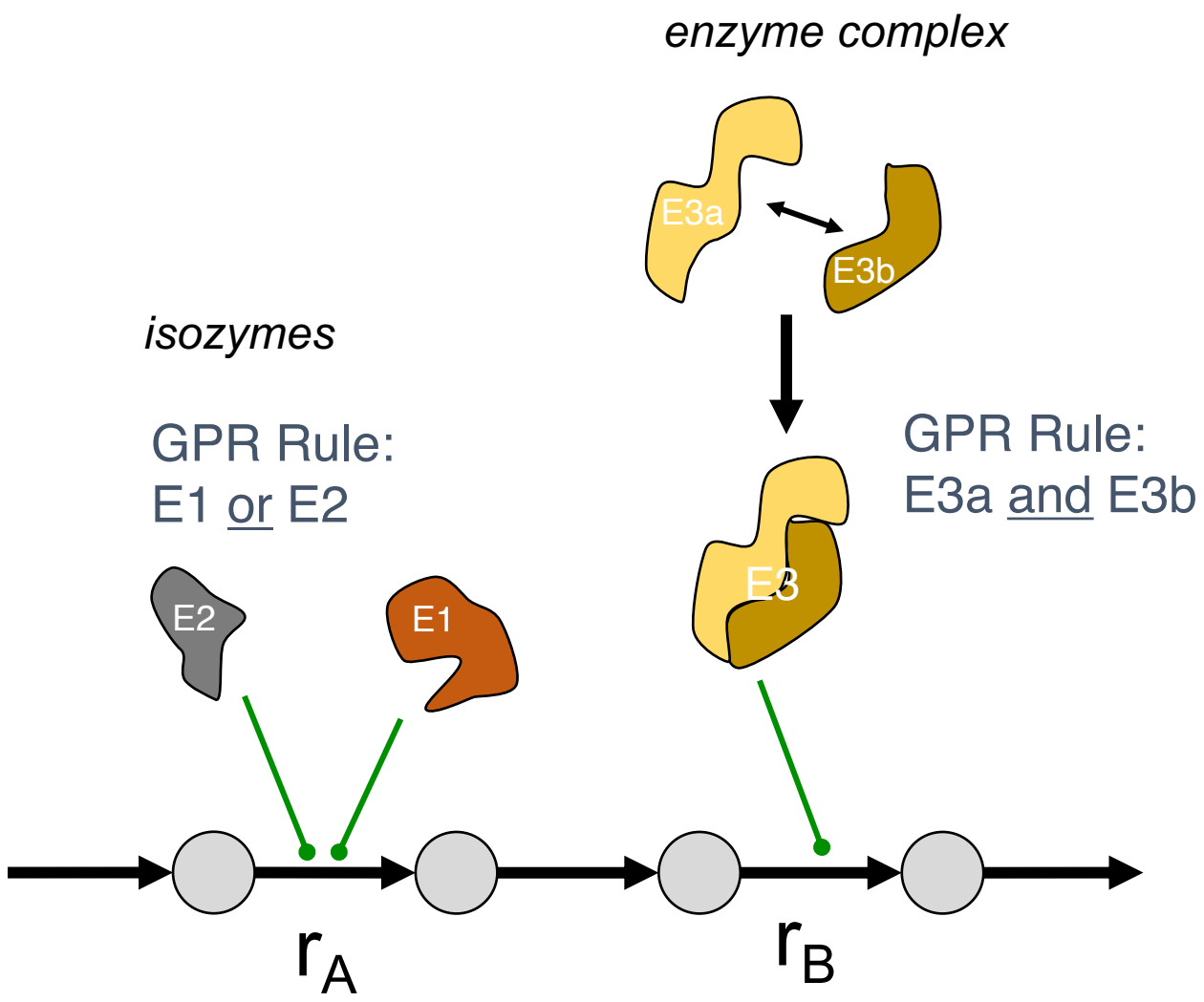
2nd matrix

Gene vs. Reaction

									…	**external IDs**
						…	…	…	…	…	**Name**
KEGG ID	**Compartment**	**Name**	**Symbol**	r1	r2	r3	r4	r5		**IDs**
C00668	cytosol [c]	glucose 6-phosphate	G6P	**−1**	0	0	0	0		
C00085	cytosol [c]	fructose 6-phosphate	F6P	**1**	**−1**	**1**	0	0		
C00354	cytosol [c]	fructose-1,6-bisphosphate	FBP	0	**1**	**−1**	**−1**	0		
C00111	cytosol [c]	dihydroxyacetone phosphate	DHAP	0	0	0	**1**	**−1**		
C00118	cytosol [c]	glyceraldehyde 3-phosphate	G3P	0	0	0	**1**	**1**		

S

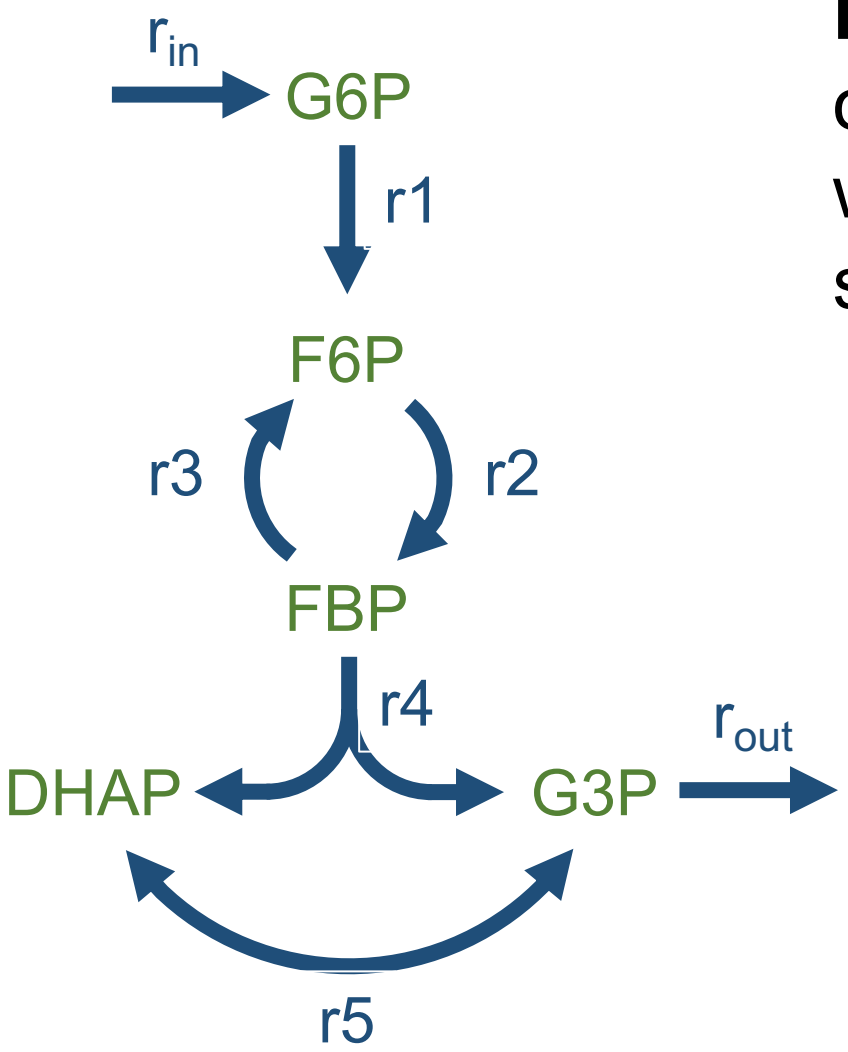
Gene-Protein-Reaction rules (GPR rules)



GPR Rules enable more accurate simulation of gene inactivation/knock-out

Knockout	Effect
E1	none
E2	none
E1 + E2	rA inactive
E3a	rB inactive
E3b	rB inactive
E3a + E3b	rB inactive

Flux Balance Analysis (FBA)



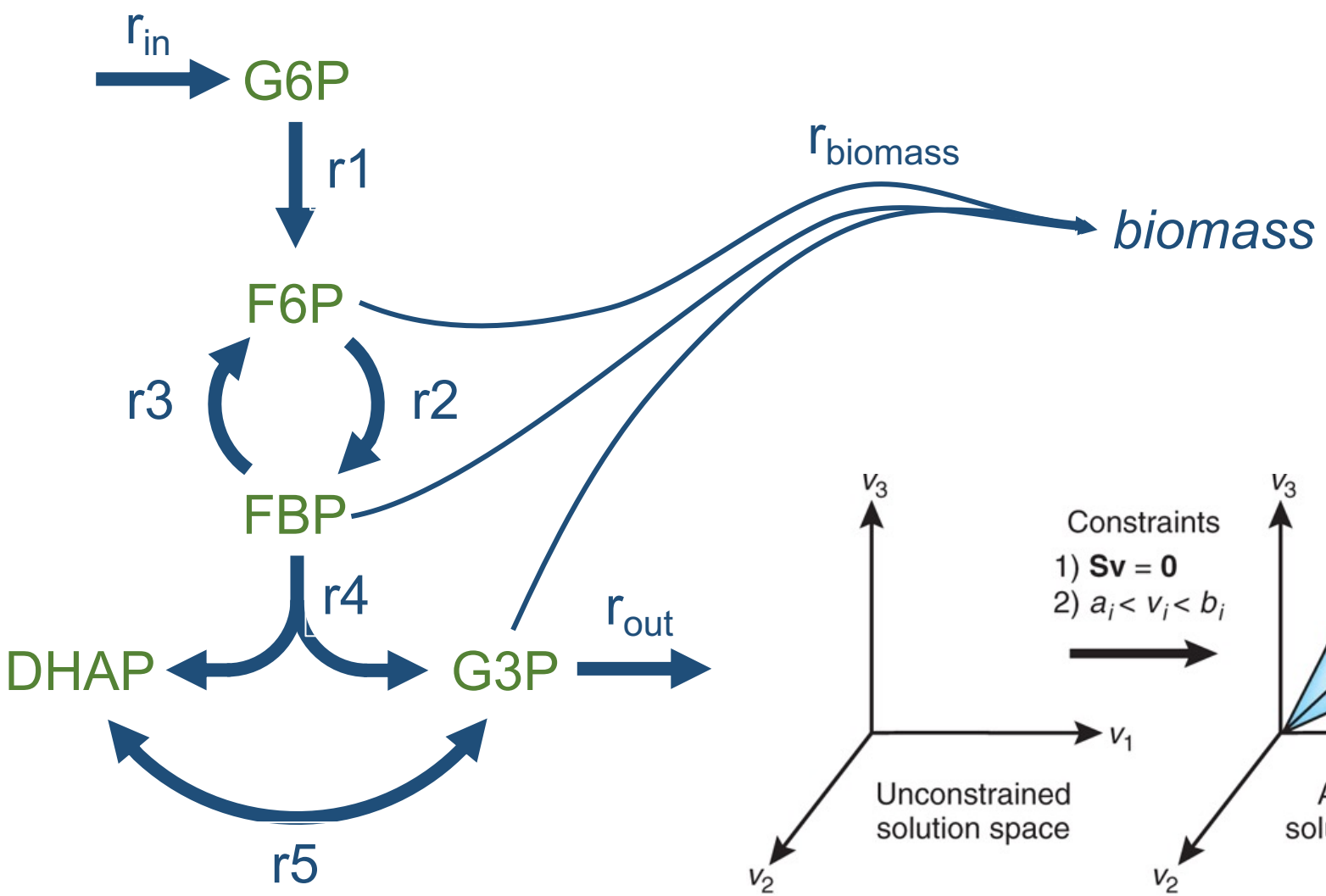
FBA seeks to calculate the reaction **fluxes** (***v***) of a network with a steady state assumption, where metabolite concentrations remain the same with respect to time

$$\frac{dX}{dt} = -v_{in} - v_{out} = 0$$

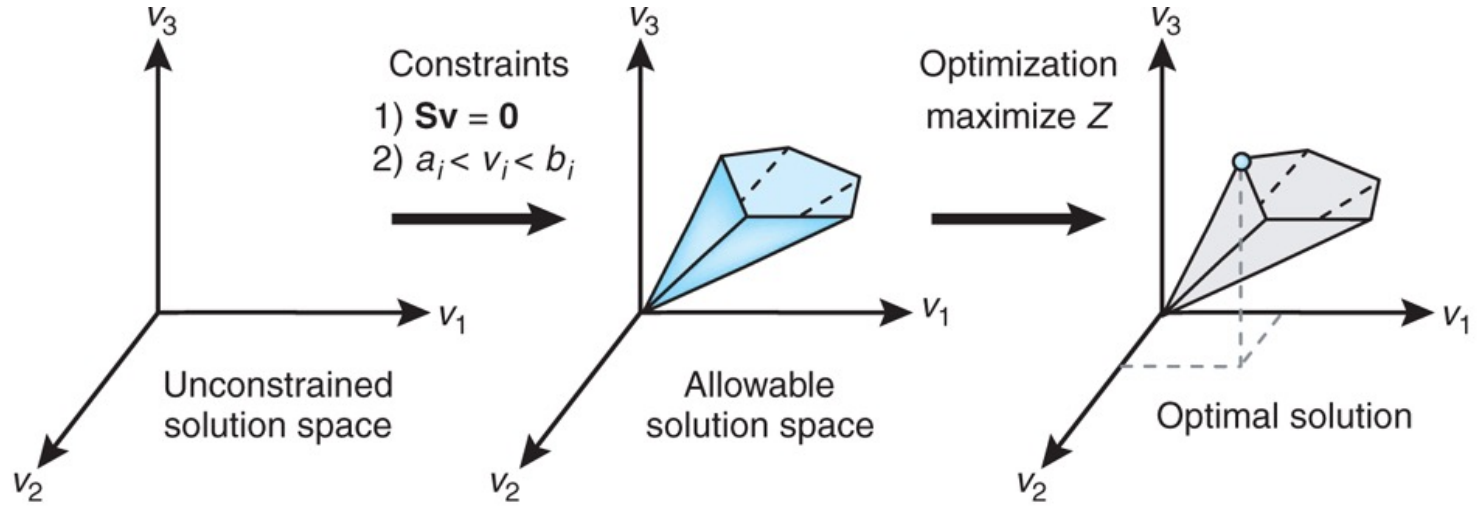
$$\frac{d[G6P]}{dt} = -v_1 + v_{in}$$

$$\frac{d[G3P]}{dt} = v_4 + v_5 - v_{out}$$

FBA using a GEM



The optimization objective usually is to maximize flux through an artificial "**biomass**" reaction, or to maximize **production of ATP**.

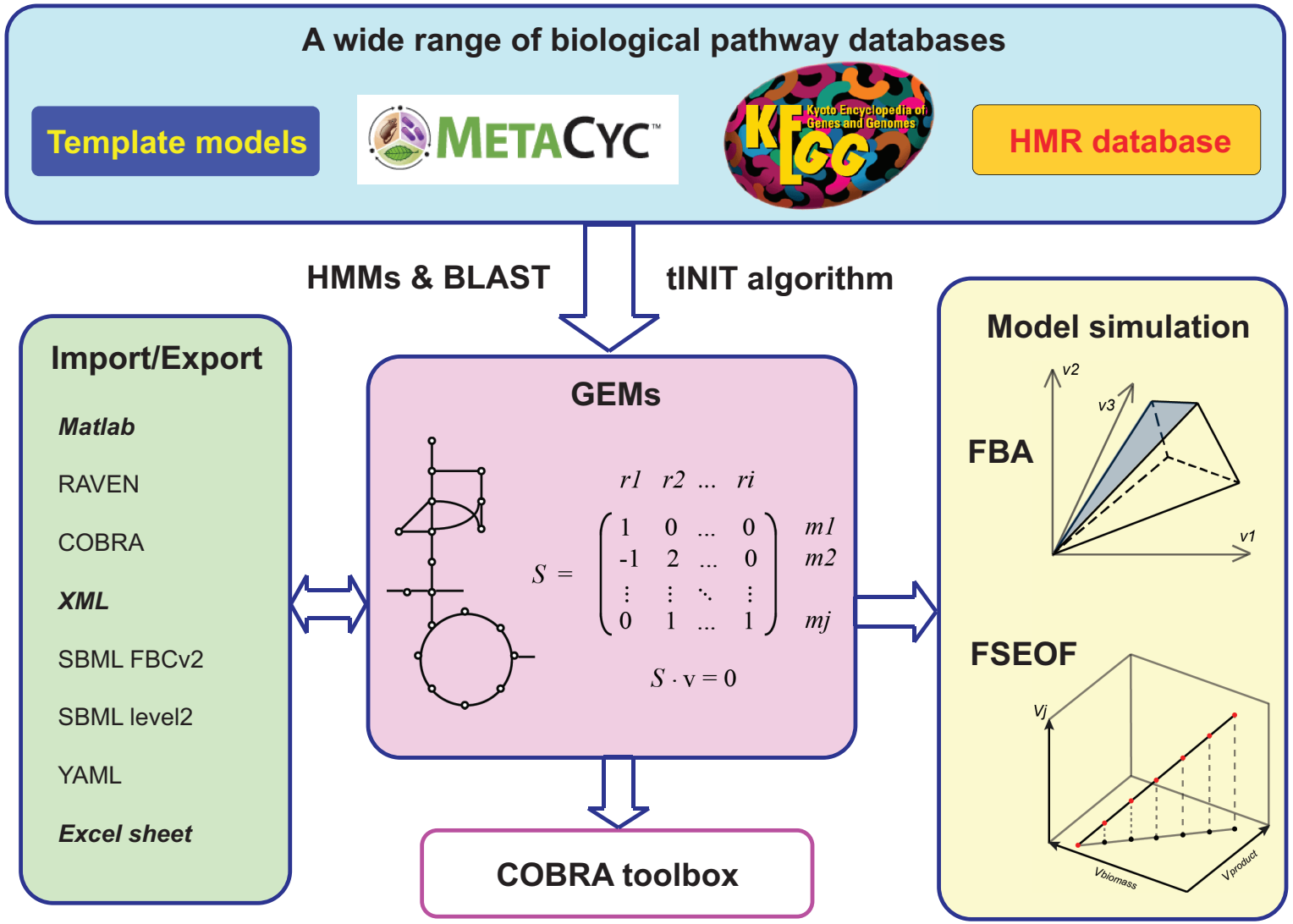


FBA currently has limited use for multicellular organisms.

GEM reconstruction and curation

THE RAVEN TOOLBOX 2

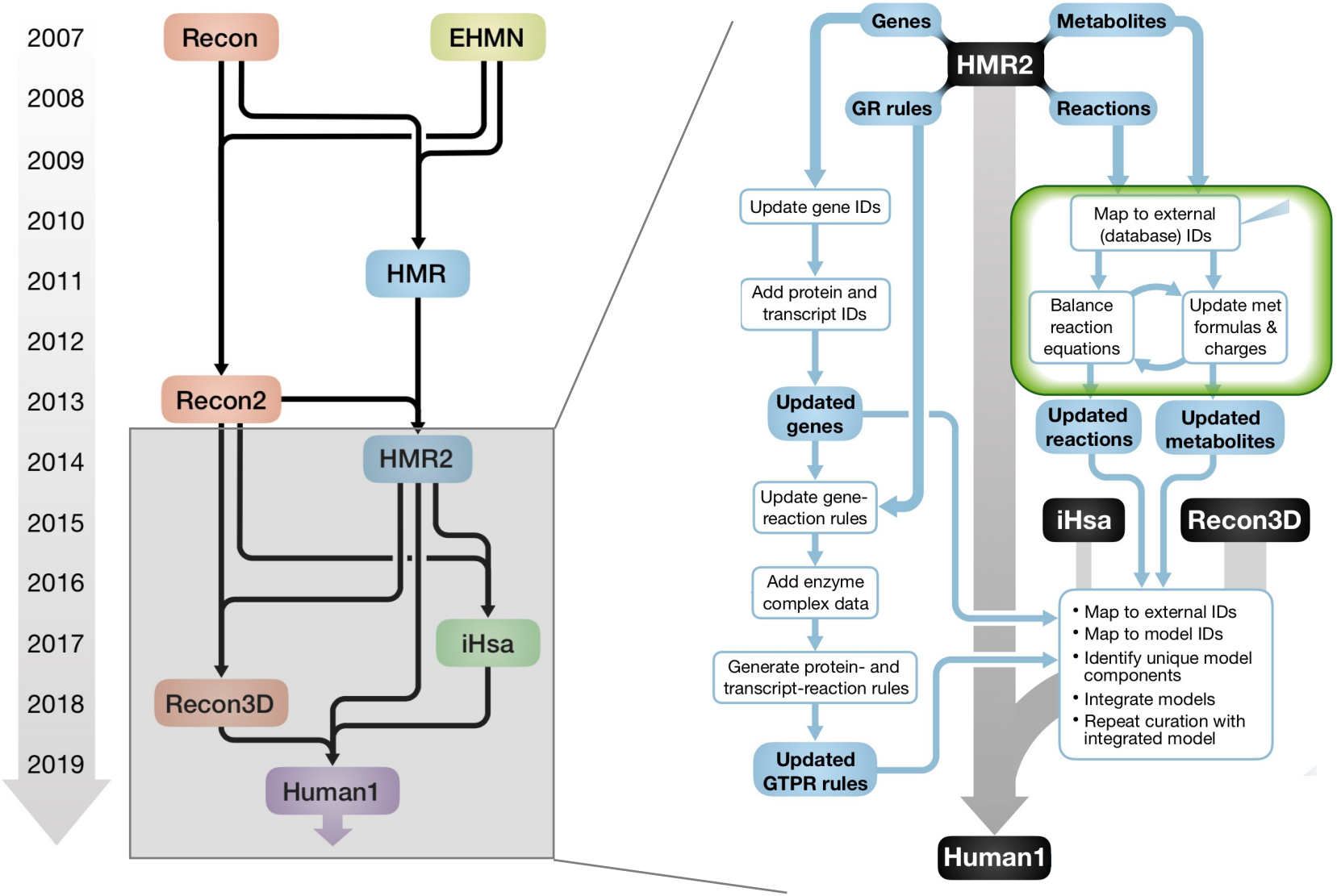
RAVEN: a toolbox for metabolic network *de novo* reconstruction and curation



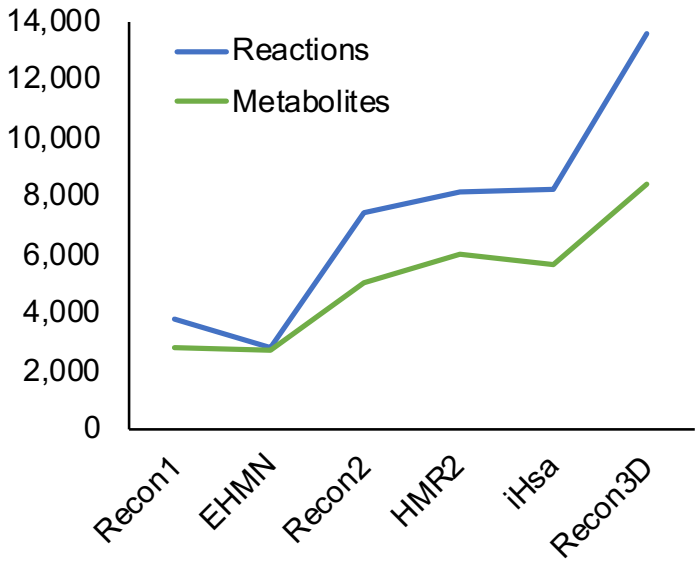
https://github.com/SysBioChalmers/RAVEN

PLOS Comp. Biol.. 2018 76:3097-3105

Human1 generation

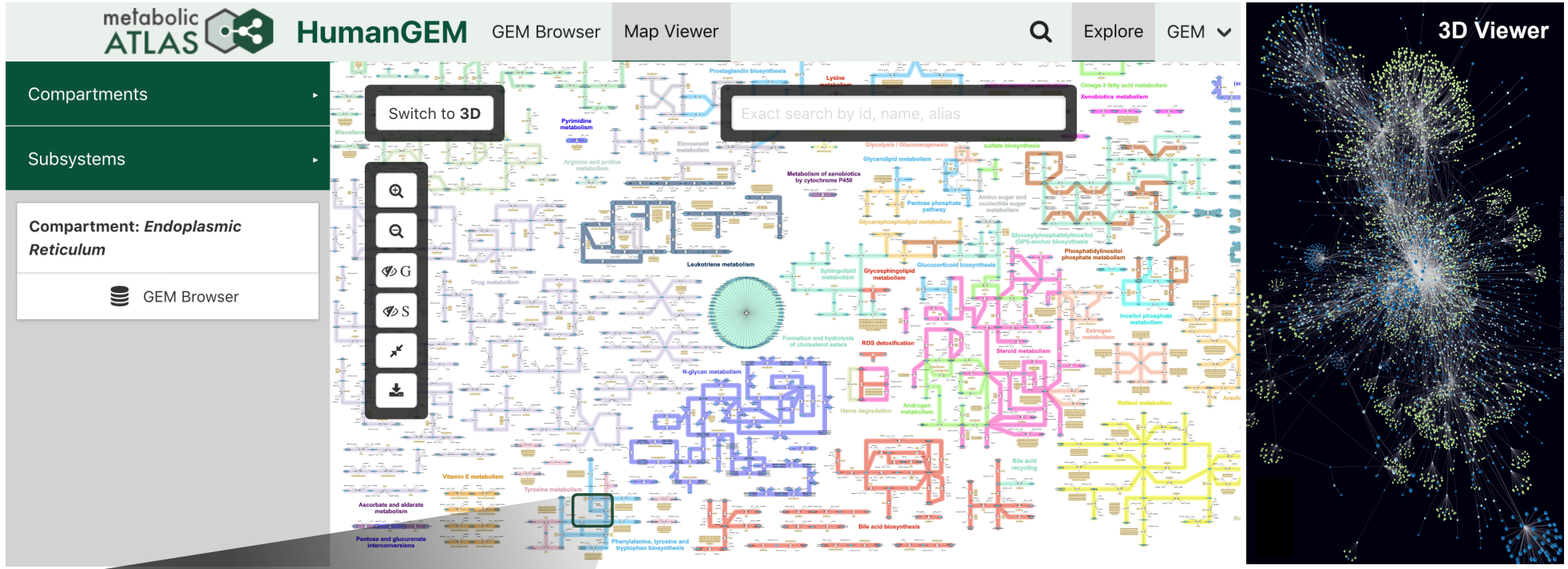


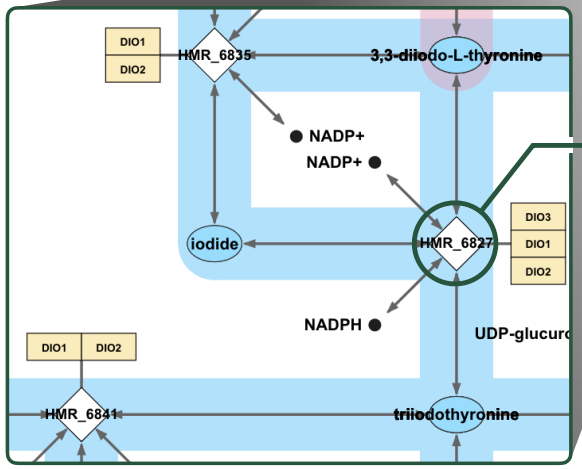
Quantity over quality



Sci Signal. 2020 13:eaaz1482

Metabolic Atlas

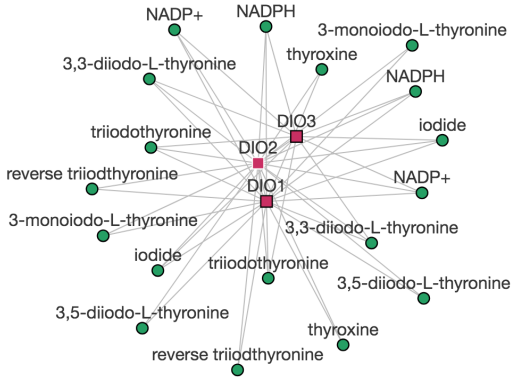




GEM Browser

HumanGEM ID	HMR_6827
Equation	3,3-diiodo-L-thyronine + iodide + NADP+ ⇔ NADPH + triiodothyronine
Reversible	Yes
Quantitative	Lower bound: -1000 - Upper bound: 1000
Genes	DIO3 or DIO2 or DIO1
EC	EC:1.97.1.10; EC:1.97.1.11
Compartment	Endoplasmic reticulum
Subsystem	Phenylalanine, tyrosine and tryptophan biosynthesis

DIO2 Interaction Partners



https://metabolicatlas.org/

Human1 on GitHub and Zenodo

SysBioChalmers / Human-GEM Public

Unwatch 13 | Unstar 40 | Fork 15

Code | Issues 22 | Pull requests 1 | Discussions | Actions | Projects 1 | Wiki | Security | Insights | Settings

main | 3 branches | 38 tags | Go to file | Add file | Code

Hao-Chalmers chore: new version 8580072 29 days ago 1,473 commits

.deprecated	chore: rename occurrences of master to main	2 months ago
.github	Merge branch 'develop' into fix/merge_dup_mets	last month
code	Human 1.9	29 days ago
data	feat: add deprecated metabolite info to tsv file	last month
model	chore: new version	29 days ago
.gitattributes	feat: use .gitattributes settings for line endings	2 months ago
.gitignore	Merge branch 'devel' into rxnAssoc	4 years ago
.standard-GEM.md	chore: rename occurrences of master to main	2 months ago
LICENSE.md	fix: replace MIT license with CC-BY	4 years ago
README.md	chore: new version	29 days ago
version.txt	chore: new version	29 days ago

README.md

Human-GEM: The generic genome-scale metabolic model of *Homo sapiens*

chat on gitter | version 1.9.0 | DOI 10.5281/zenodo.5186414

About

The generic genome-scale metabolic model of Homo sapiens

sysbiochalmers.github.io/human-ge...

human-metabolism | genome-scale-models | standard-gem

Readme

CC-BY-4.0 License

Releases 38

Human 1.9.0 Latest
29 days ago

+ 37 releases

Contributors 9

Languages

MATLAB 98.1% | Python 1.9%

August 12, 2021

Software | Open Access

SysBioChalmers/Human-GEM: Human 1.9.0

Hao Wang; Jonathan Robinson; Mihail Anton; Cholley Pierre-Etienne; Pinar Kocabas; PkiwiBird; pecholley; Jorge Ferreira; Pranas Grigaitis

- Style (PR #294):
  - add and reformat citations in README
- Fixes (PR #292):
  - replace deprecated Ensembl gene ids with updated ones, as reported in #278
  - update `genes.tsv` annotation file using script `fetch_ensembl_gene_annotations`
- Features (PR #291):
  - adjust `sanityCheck` script to enable the detection of reusing deprecated MA ids, as discussed in #265
- Fixes (PR #290):
  - fix the ATP hydrolysis stoichiometry in biomass equation `MAR13082`, as reported in #289.
- Fixes (PR #287):
  - refactor `fetch_ensembl_gene_annotations.py` script to allow retrieving annotations with empty gene symbols or ENSP ID, and to show the replacement Ensembl IDs for deprecated ones, as proposed in #278
- Features (PR #286):
  - introduces a GH Action for testing the yaml conversion with `testYamlConversion`.
- Fixes (PR #285):
  - fix: merge duplicated long-chain fatty acyl-CoA mets, as reported in #268, #269
- Style (PR #284):
  - rename default branch (`master` --> `main`) as discussed in #226
  - change default branch names in repo documents and code
- Fixes (PR #283):
  - remove cytosolic protons from reaction in other subcellular compartments, as detailed in #282
    - revise `MAR05259` by replacing proton with lysosomal version
    - remove `MAR04758` that is duplicate to `MAR01044`
    - remove `MAR01459` that is duplicate to `MAR02041`, whose proton is replaced with the mitochondrial version
- Fixes (PR #281):
  - excluded gene `ENSG00000197375` from MAR02590 (carnitine shuttle), due to lack of evidence (#279)
- Style (PR #275):
  - add `.gitattributes` file to ensure consistent `LF` line endings as discussed in #264
- Features (PR #274):
  - add `rxnNotes` field to Human-GEM, as planned in #272
  - adjust `importYaml` / `exportYaml` functions to enable handling of `rxnNotes` field

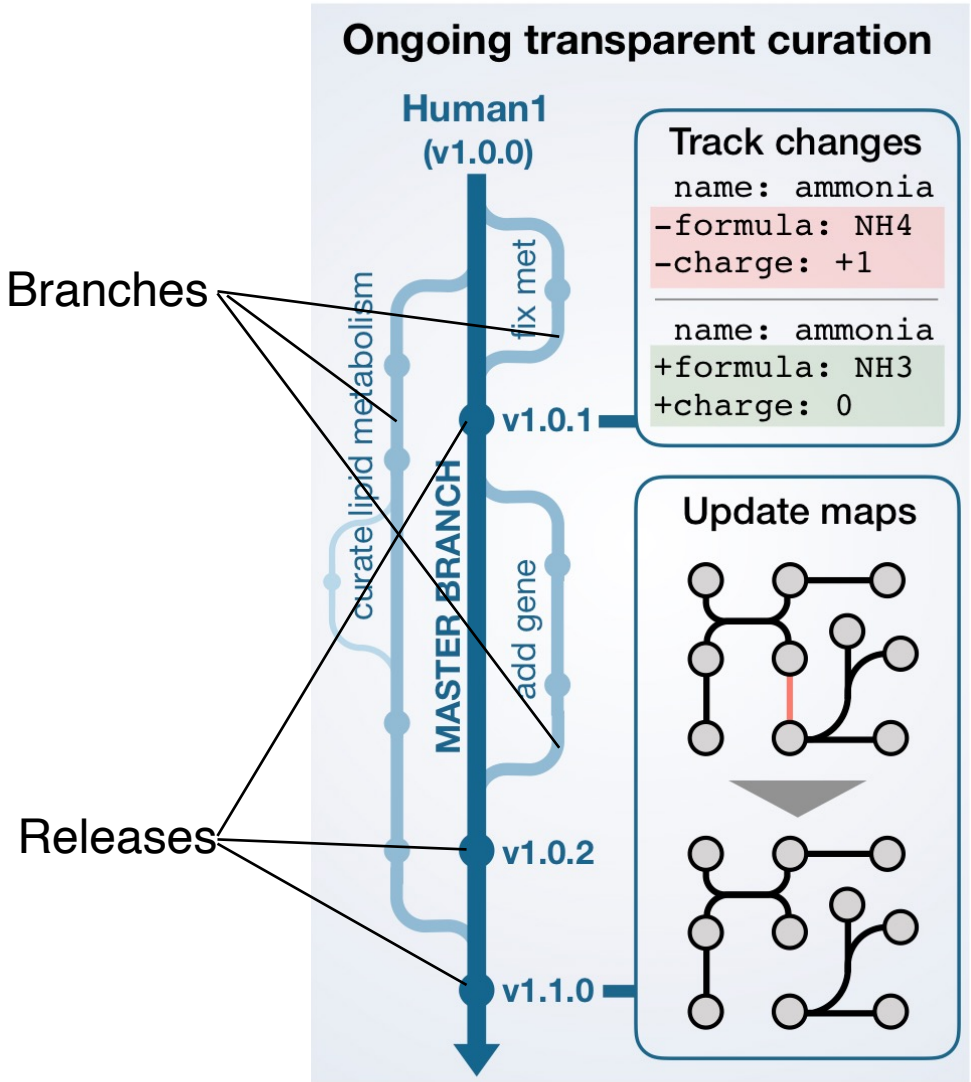
https://github.com/SysBioChalmers/Human-GEM

https://doi.org/10.5281/zenodo.4099692

GEM curation on GitHub

- **Git** is a distributed version-control system
  - Support collaborative work
  - Easy tracking of changes and resolving conflicts
  - Branching and merging

- **GitHub** is a webserver hosting git-based repositories
  - Manage git operations by web browsing
  - Issues: report bugs, request features
  - Branch management (master, devel, feature/fix)
  - Making pull requests (PR) for merging branch



https://github.com/SysBioChalmers/Human-GEM

Issue-guided curations on GitHub

Gene association has been identified for a mitochondrial transporter #109

Closed **avlant** opened this issue on May 9 · 5 comments

avlant commented on May 9 Collaborator

Description of the issue:

A mitochondrial amino acid transporter (ENSG00000164466) has recently been id ied [1]. It transports serine and alanine, and should therefore be associated with HMR_5113 a MR_5114.

[1] PubMed: 30442778, https://www.uniprot.org/uniprot/Q9H9B4

Expected feature/value/output:

HMR_5113 m01307c -> m01307m 0.00 1000.00 0.00 ENSG00000164466
HMR_5114 m02896c -> m02896m 0.00 1000.00 0.00 ENSG00000164466

1

Hao-Chalmers added the enhancement label on May 9

Hao-Chalmers self-assigned this on May 9

https://github.com/SysBioChalmers/Human-GEM/issues/109

Discussion …

Hao-Chalmers commented on May 9 • edited — Member

@avlant thanks for providing the literature that reveals newly identified mitochondrial transporter SFXN1 (ENSG00000164466) for serine.

Here are some questions regarding the proposed changes:

1. In addition to SFXN1, its homolog SFXN3 (ENSG00000107819) was shown with equivalent function and can compensate to SFXN1 loss. Would it be okay to have both as isoenzymes: `ENSG00000164466 or ENSG00000107819`?
2. The other substrate alanine (m01307) was speculated from *in invtro* analysis without concrete evidence. Based on this particular citation, should we leave out the change to HMR_5113?

avlant commented on May 16 — Author — Collaborator

@Hao-Chalmers. I relied on the UniProt annotation "Also able to transport other amino-acids, such as alanine (PubMed:30442778)." [1]. But if alanine transport is speculative, then it is probably better to leave it out.

[1] https://www.uniprot.org/uniprot/Q9H9B4

Hao-Chalmers commented on May 16 • edited — Member

@avlant one option to distinguish the varied evidence level is by assigning them with different `confidenceScore` in the model, such as using `4` (direct biochemical evidence) for HMR_5114 and `2` (indirect evidence) for HMR_5113.

Below is the `SFXN3` UniProt annotation that is same to `SFXN1`, it also points to the same reference (PubMed:30442778).

https://www.uniprot.org/uniprot/Q9BWM7

https://github.com/SysBioChalmers/Human-GEM/issues/109

Implementation

Hao-Chalmers added a commit that referenced this issue on May 20

`feat: add new gene associations according to #109` `d3fadd3`

Hao-Chalmers added a commit that referenced this issue on Jun 11

`chore: update humanGEM.mat and humanGEM.yml` ··· `59104eb`

```
This update is implemented by running command:
`updateGrRules('associateMitoImporter_20190520.tsv', 7, 3, true);`
- 2 newly identified amino acid importers are added for 2 transport reactions, to
address #109
- the corresponding reference and confidence scores are also updated, together with the
relevant gene and protein fields
```

Hao-Chalmers referenced this issue on Jun 12

Human v1.1.0 #121 Merged

Hao-Chalmers closed this on Jun 13

https://github.com/SysBioChalmers/Human-GEM/issues/109

Intertwined and recursive curation tasks

	Curation tasks	Issues	Pull requests	#Release
Rxn/Met	Rxn/Met association/annotation		#1, #2, #4, #5, #6	4
Gene/Rxn	Gene and grRules curation	#7, #15, #68	#8, #9, #12, #24, #32, #51, #83, #84	8
Gene/Rxn/Met	**Recon3D** integration		#17	1
	Standardize model fields		#19, #39, #76, #95	4
Rxn/Met	Migrate toward a binary-free mode	#27, #71, #75	#79	1
Gene/Rxn/Met	Inner mitochondrial compartment		#42	1
Rxn/Met	Pseudoreactions	#28	#72, #90	2
Rxn/Met	Mass/energy leak	#33	#62, #69	2
Rxn/Met	Removal of duplicated reactions	#43, #44	#19, #35, #42, #72	4
Gene/Rxn	Incorporation enzyme complexes	#29, #89	#17, #19, #32, #84	4
Gene/Rxn	Reaction confidence/reference	#48	#52	2
Rxn/Met	Reaction balancing	#49, #58, #60	#16, #21, #23, #30, #52, #81	4
Gene/Rxn/Met	Subsystems consolidation	#50	#56	1
Rxn/Met	Biomass reactions	#63	#76	1
Gene/Rxn/Met	Map-related curation	#87	#66	1

Biology | Git(Hub)

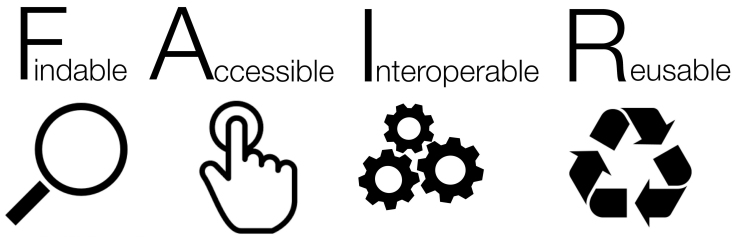
Yaml-based curation workflow

A rich collection of published file formats

Human-GEM is published and distributed as:

These files are either hard to track changes (xlsx and mat files are binary) or difficult to have visible history (txt is incomplete and xml is overwhelmed with attribute tags)

GEM Reproducibility and FAIR-ness



Why Yaml file?

SBML (.xml)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xmlns:groups="http://www.sbml.org/sbml/level3/version1/groups/version1" level="3" version="1" fbc:required="false" groups:required="false">
  <model metaid="HumanGEM" id="HumanGEM" name="Generic genome-scale metabolic model of Homo sapiens" fbc:strict="true">
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      <body xmlns="http://www.w3.org/1999/xhtml">
        <p>Genome-scale metabolic models are valuable tools to study metabolism and provide a scaffold for the integrative analysis of omics data. This is the latest version of Human-
GEM, which is a genome-scale metabolic model of a generic human cell. The objective of Human-GEM is to serve as a community model for enabling integrative and mechanistic
studies of human metabolism.</p>
      </body>
    </notes>
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xmlns:vCard4="http://www.w3.org/2006/vcard/ns#" xmlns:bqbiol="http://biomodels.net/biology-qualifiers/" xmlns:bqmodel="http://biomodels.net/model-qualifiers/">
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```


YAML (.yml)


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- metaData:
    short_name: "Human-GEM"
    full_name: "Generic genome-scale metabolic model of Homo sapiens"
    version: "1.5.0"
    date: "2020-10-17"
    authors: "Jonathan Robinson, Hao Wang, Pierre-Etienne Cholley, Pinar Kocabas"
    email: "jonrob@chalmers.se"
    organization: "Chalmers University of Technology"
    taxonomy: "9606"
    github: "https://github.com/SysBioChalmers/Human-GEM"
    description: "Genome-scale metabolic models are valuable tools to study metabolism and provide a scaffold for the integrative analysis of omics data. This is the latest version of
Human-GEM, which is a genome-scale metabolic model of a generic human cell. The objective of Human-GEM is to serve as a community model for enabling integrative and
mechanistic studies of human metabolism."
- metabolites:
  - !!omap
    - id: "m00001c"
    - name: "(-)-trans-carveol"
    - compartment: "c"
    - formula: "C10H16O"
    - charge: 0
    - inchis: ""
    - metFrom: "HMRdatabase"
  - !!omap
    - id: "m00001s"
    - name: "(-)-trans-carveol"
    - compartment: "s"
    - formula: "C10H16O"
    - charge: 0
    - inchis: ""
    - metFrom: "HMRdatabase"
  - !!omap
    - id: "m00002c"
    - name: "(+)-alpha-pinene"
    - compartment: "c"
    - formula: "C10H16"
    - charge: 0
    - inchis: ""
    - metFrom: "HMRdatabase"
  - !!omap
    - id: "m00002s"
    - name: "(+)-alpha-pinene"
    - compartment: "s"
    - formula: "C10H16"
    - charge: 0
    - inchis: ""
    - metFrom: "HMRdatabase"
  - !!omap
    - id: "m00003c"
    - name: "(10Z)-heptadecenoic acid"
    - compartment: "c"
    - formula: "C17H31O2"
    - charge: -1
    - inchis: ""
    - metFrom: "HMRdatabase"
  - !!omap
    - id: "m00003l"
    - name: "(10Z)-heptadecenoic acid"
    - compartment: "l"
    - formula: "C17H31O2"
    - charge: -1
    - inchis: ""
    - metFrom: "HMRdatabase"
  - !!omap
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    - name: "(10Z)-heptadecenoic acid"
    - compartment: "r"
    - formula: "C17H31O2"
```


- With complete information
- No special tags/characters
- Line-based
- Supported by RAVEN/Cobra

release	# rxns	# mets	# genes	date	Pull request
v0.1.0	*8181*	*6006*	*3705*	2018-08-24	**#14**
v0.2.0	*14835*	*8884*	*4022*	2018-09-05	**#17**
v0.3.0	*13850*	*10082*	*4069*	2018-09-18	**#19, #20**
v0.3.1	*13848*	*10082*	*4071*	2018-09-22	**#23, #24**
v0.4.0	*13848*	*10131*	*4071*	2018-10-01	**#30**
v0.4.1	*13757*	*10131*	*4071*	2018-10-06	**#32, #32, #35**
v0.4.2	*13759*	*10131*	*4071*	2018-10-12	**#39**
v0.5.0	*13755*	*10131*	*4071*	2018-10-16	**#42**
v0.5.1	*13755*	*10131*	*3949*	2018-10-19	**#51, #52**
v0.5.2	*13755*	*10131*	*3949*	2018-10-28	**#56**
v0.6.0	*13519*	*10131*	*3949*	2018-11-11	**#59, #62**
v0.6.1	*13755*	*10131*	*3949*	2018-11-26	**#66, #69**
v0.7.0	*13748*	*10131*	*3949*	2018-12-15	**#72**
v0.8.0	*13774*	*10155*	*3949*	2019-01-24	**#76**
v0.8.1	*13774*	*10155*	*3949*	2019-02-01	**#79**
v0.8.2	*13774*	*10155*	*3949*	2019-02-08	**#81**
v0.8.3	*13774*	*10155*	*3919*	2019-02-21	**#84**
v1.0.0-β	*13774*	*10155*	*3627*	2019-02-26	**#83**
v1.0.0	*13520*	*10103*	*3627*	2019-03-12	**#90, #91**
v1.0.1	*13520*	*10103*	*3627*	2019-04-03	**#95, #96**
v1.0.2	*13520*	*10103*	*3627*	2019-04-19	**#103, #105**
v1.0.3	*13520*	*10103*	*3627*	2019-05-17	**#108, #110, #111**
v1.1.0	*13520*	*10103*	*3628*	2019-06-13	**#113, #116, #120**
v1.1.1	*13527*	*10111*	*3628*	2019-09-12	**#122, #123, #133**
v1.1.2	*13527*	*10111*	*3628*	2019-10-12	**#125, #132**

Human-GEM

- 101 issues
- 203 pull requests
- 40 releases
- 23 contributors
- 41 “like”
- 15 forks

Human-GEM is open-curated by research community

Contributors

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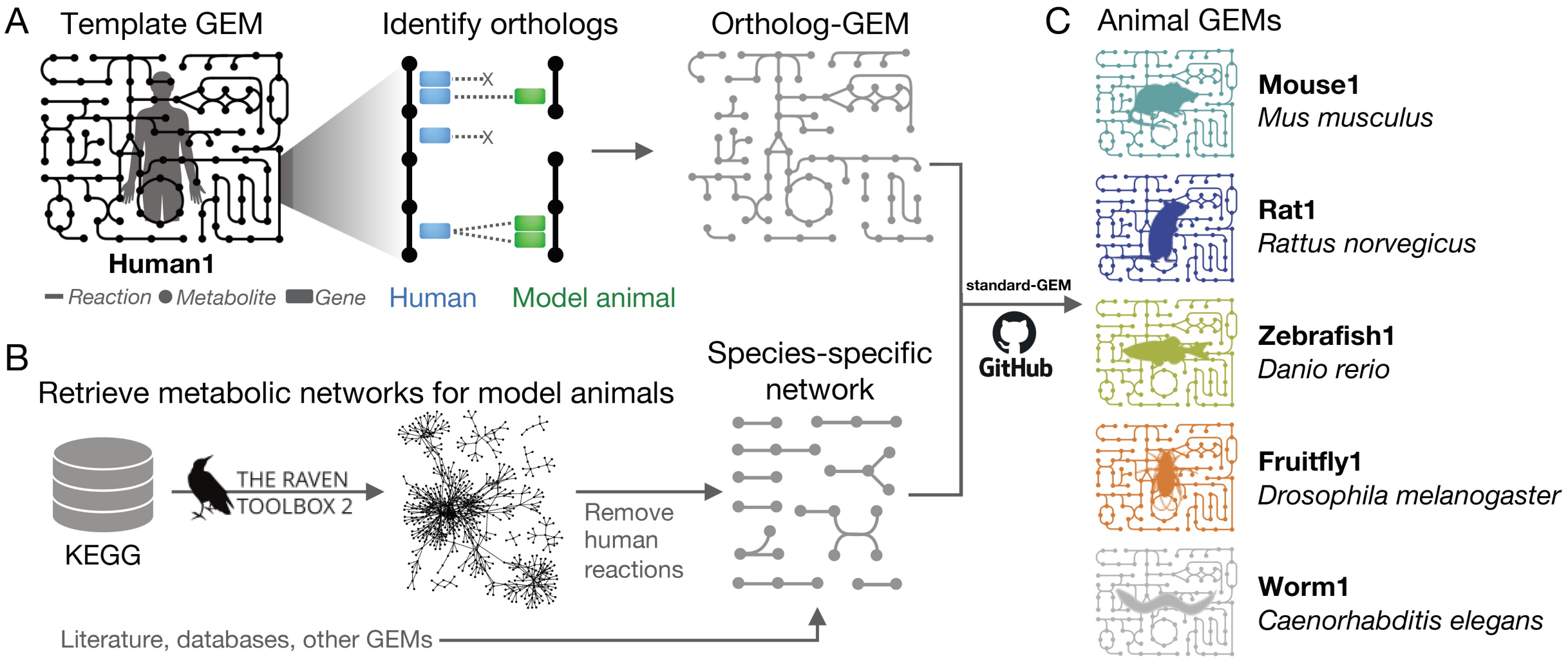
Jose L. Cadavid	Marco Pagni	Mihail Anton	Pierre-Etienne Cholley	Pierre-Etienne Cholley	PkiwiBird	Pranas Grigaitis	Pınar Kocabaş
Rasool Saghaleyni	Sarah Cherkaoui	Simonas Marcišauskas	TunahanCakir	Xuhang Li	johan-gson	smoretti	

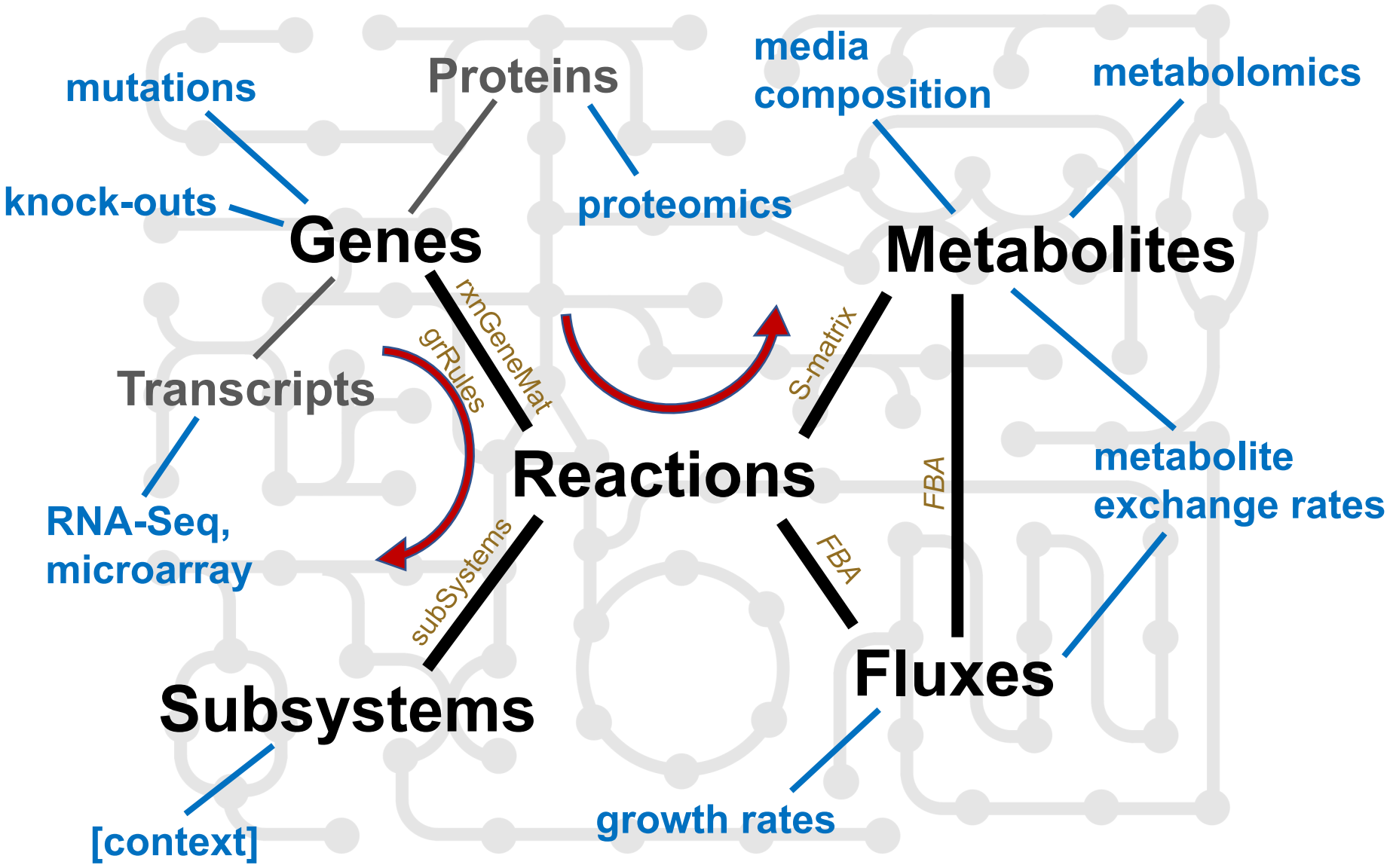
Generation of model animal GEMs



PNAS. 2021 118:e2102344118

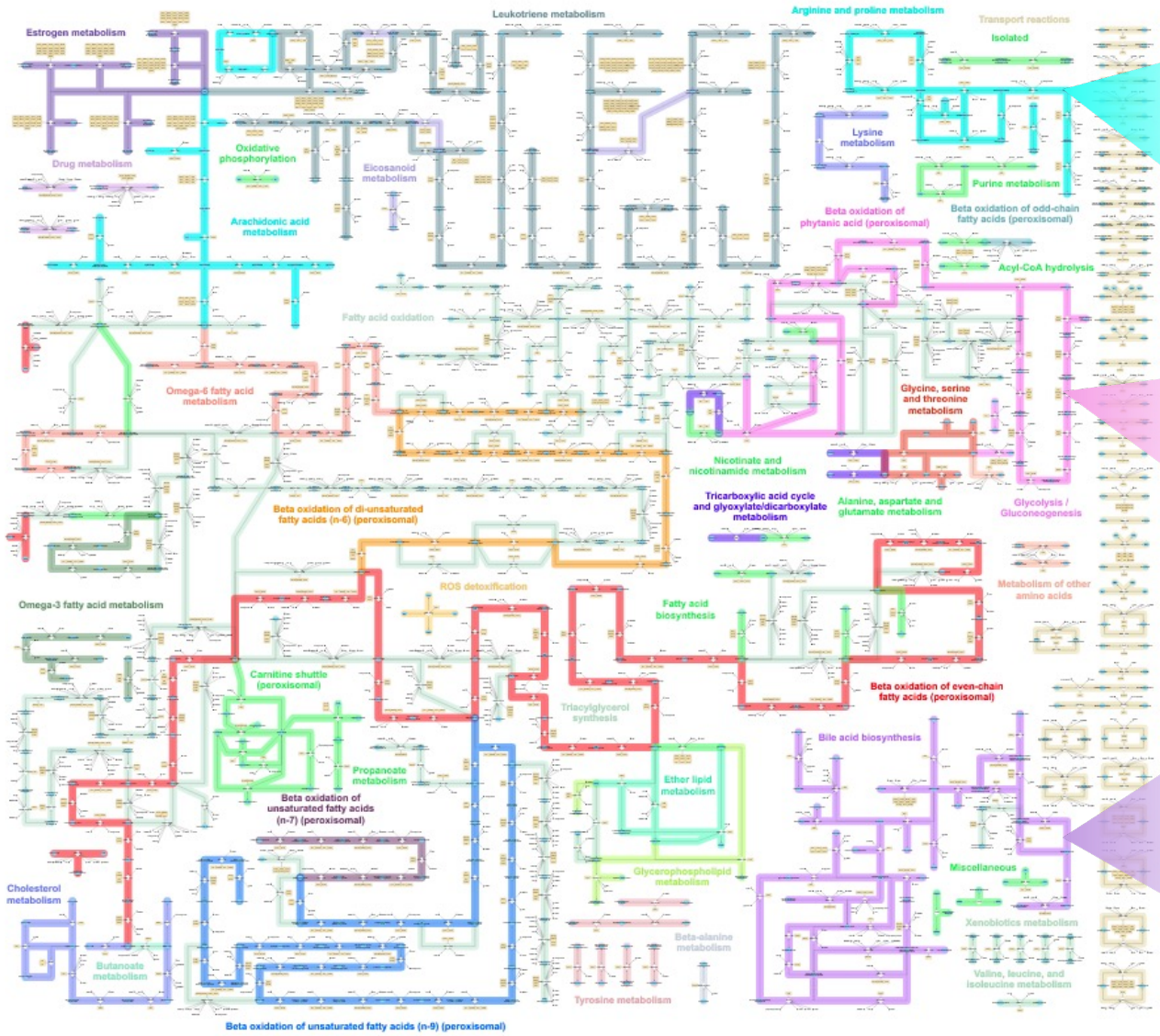
GEM Applications

GEM as an integrative tool



GEM-derived gene sets

Subsystem gene sets



Arginine and proline metabolism

ABHD14A-ACY1 ACY1 AGMAT ALDH18A1 ALDH1B1 ALDH2 ALDH3A2 ALDH4A1
ALDH7A1 ALDH8A1 ALDH9A1 AMD1 AOC1 AOC2 AOC3 ARG1 ARG2 AZIN2
CA5A CA5B CARNS1 CKB CKM CKMT1A CKMT1B CKMT2 CNDP1 CNDP2 DAO
DHPS FAR1 FAR2 GAMT GOT1 GOT2 HOGA1 LEFTY1 MAOA MAOB MTAP …

Beta oxidation of phytanic acid

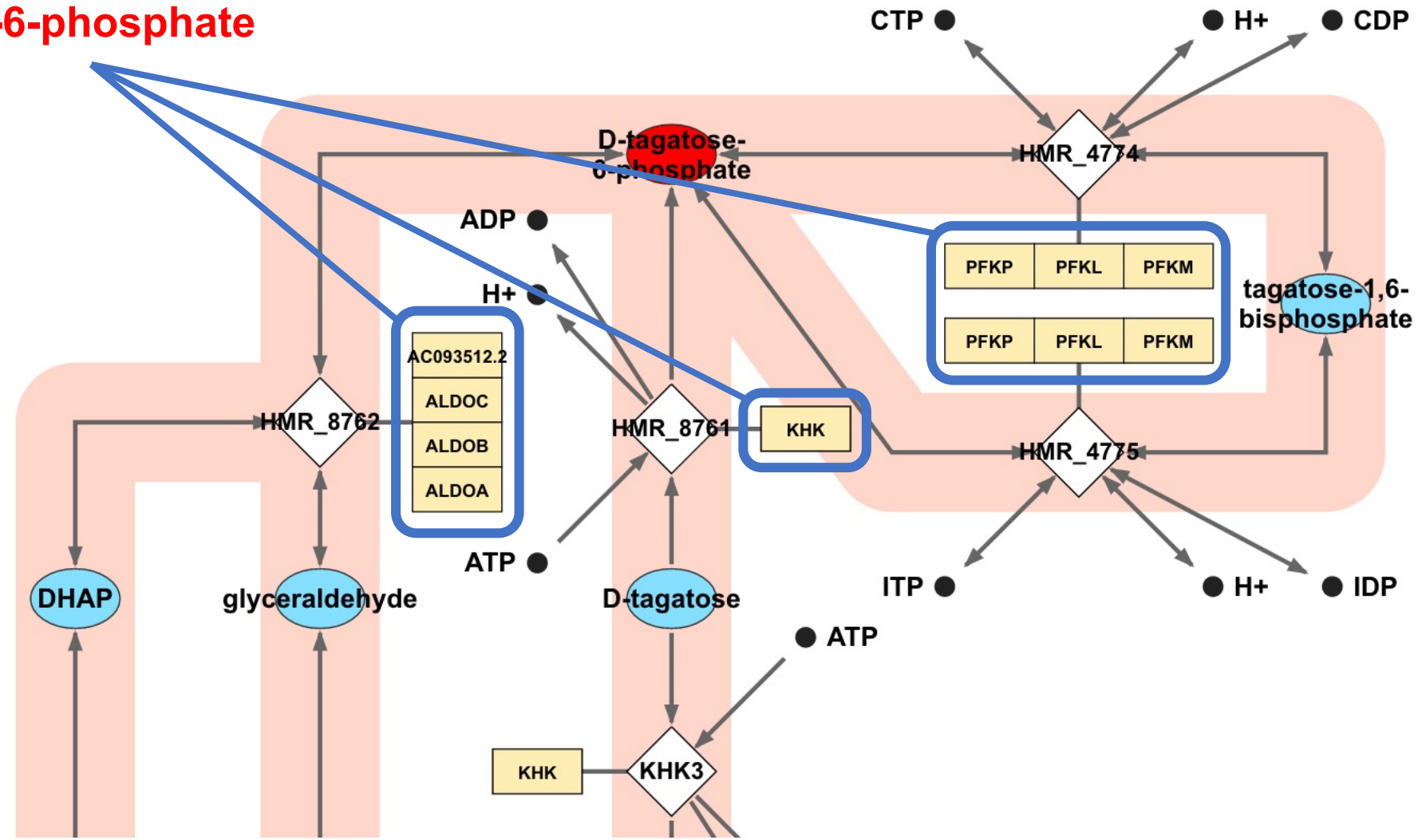
ACAA1 ACOT2 ACOT4 ACOX1 ACOX3 ACSBG1 ACSBG2 ACSL1 ACSL3 ACSL4
ACSL5 ACSL6 AMACR ECI1 ECI2 EHHADH HACL1 HADHA HSD17B4 KRTAP11-1
MEIKIN MYO5B PHYH SLC27A2 …

Bile acid biosynthesis

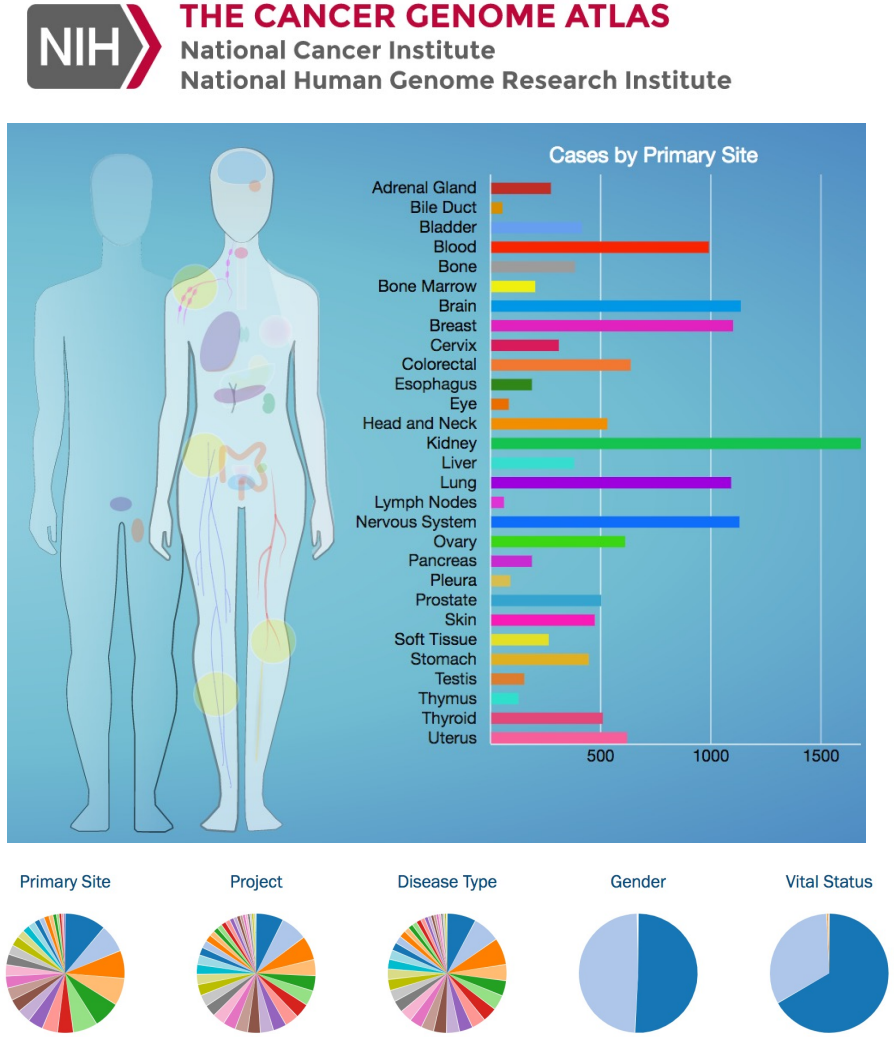
ABCB11 ABCC11 ABCC3 ABCD1 ACAA1 ACAA2 ACOT1 ACOT2 ACOT4 ACOT6
ACOT7 ACOT8 ACOX1 ACOX2 ACOX3 ADH1A ADH1B ADH1C ADH4 ADH5
ADH6 ADH7 ADHFE1 ADO AKR1B10 AKR1B15 AKR1C1 AKR1C2 AKR1C3 AKR1C4
AKR1D1 ALDH1B1 ALDH2 ALDH3A1 ALDH3A2 ALDH7A1 ALDH9A1 AMACR BAAT
BCAP31 …

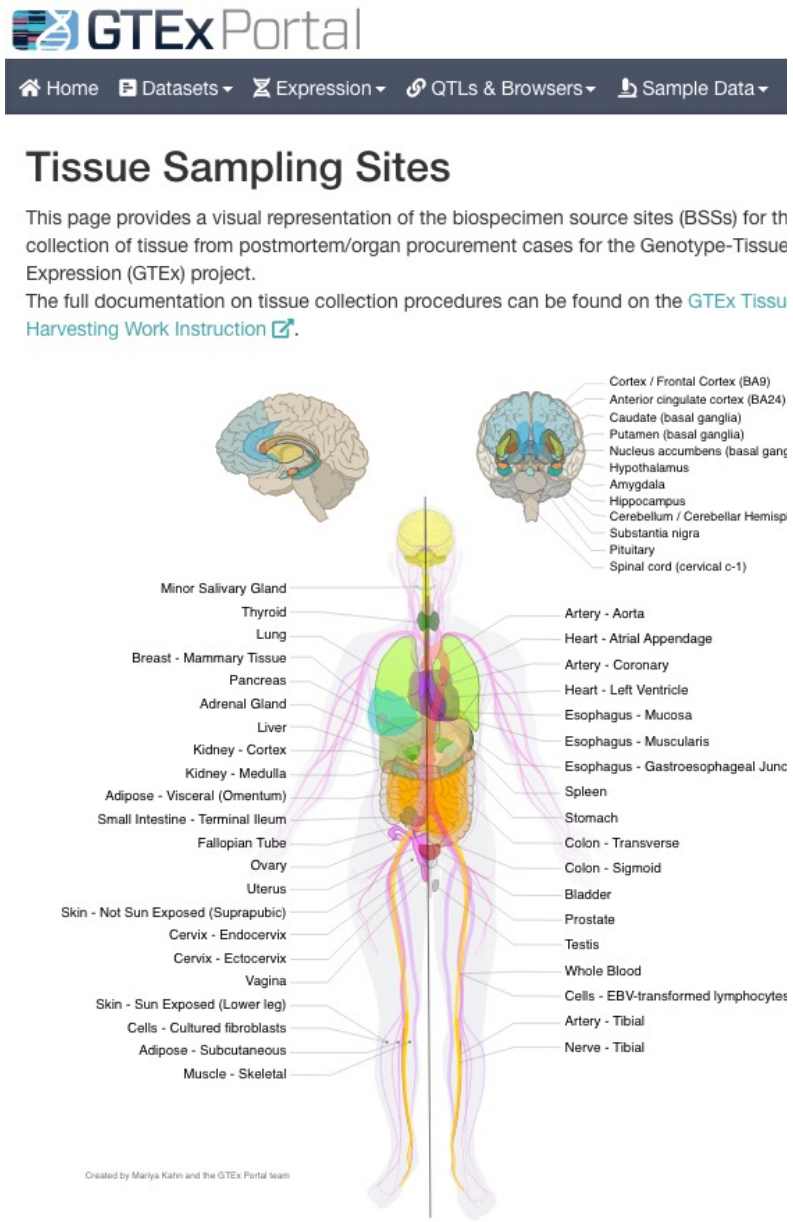
Reporter metabolite gene set

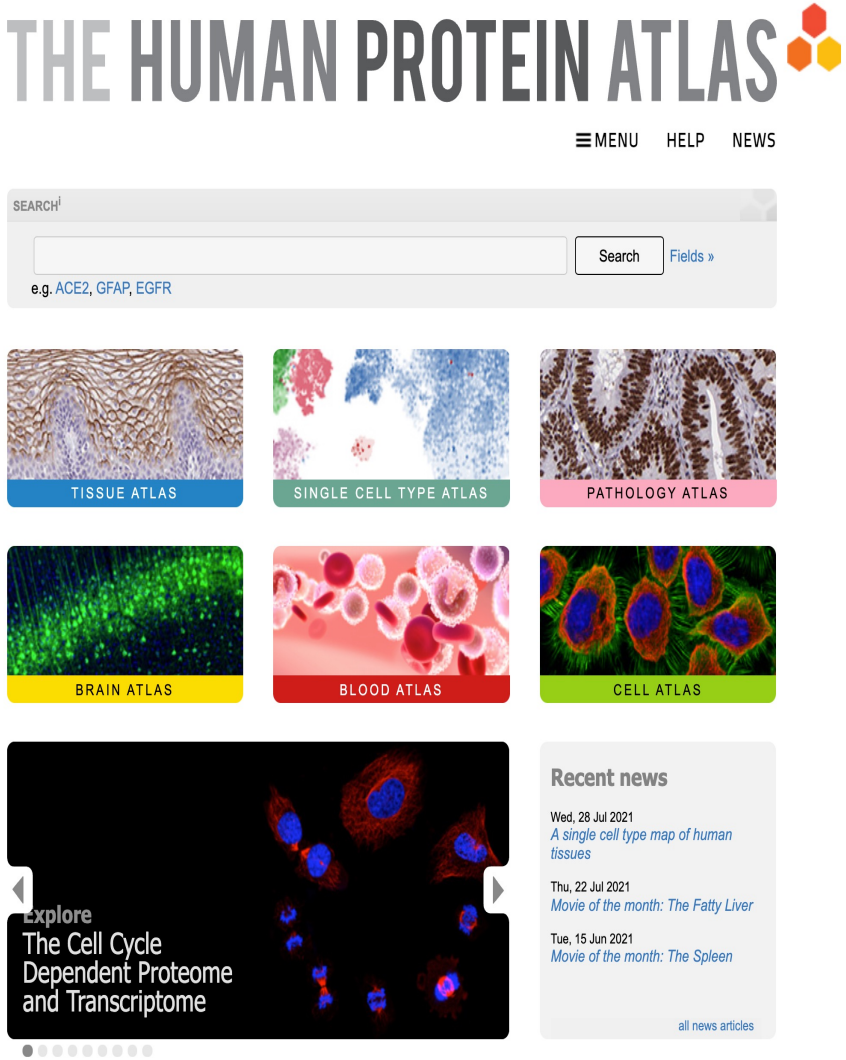
Genes associated with
D-tagatose-6-phosphate



Omics data resources

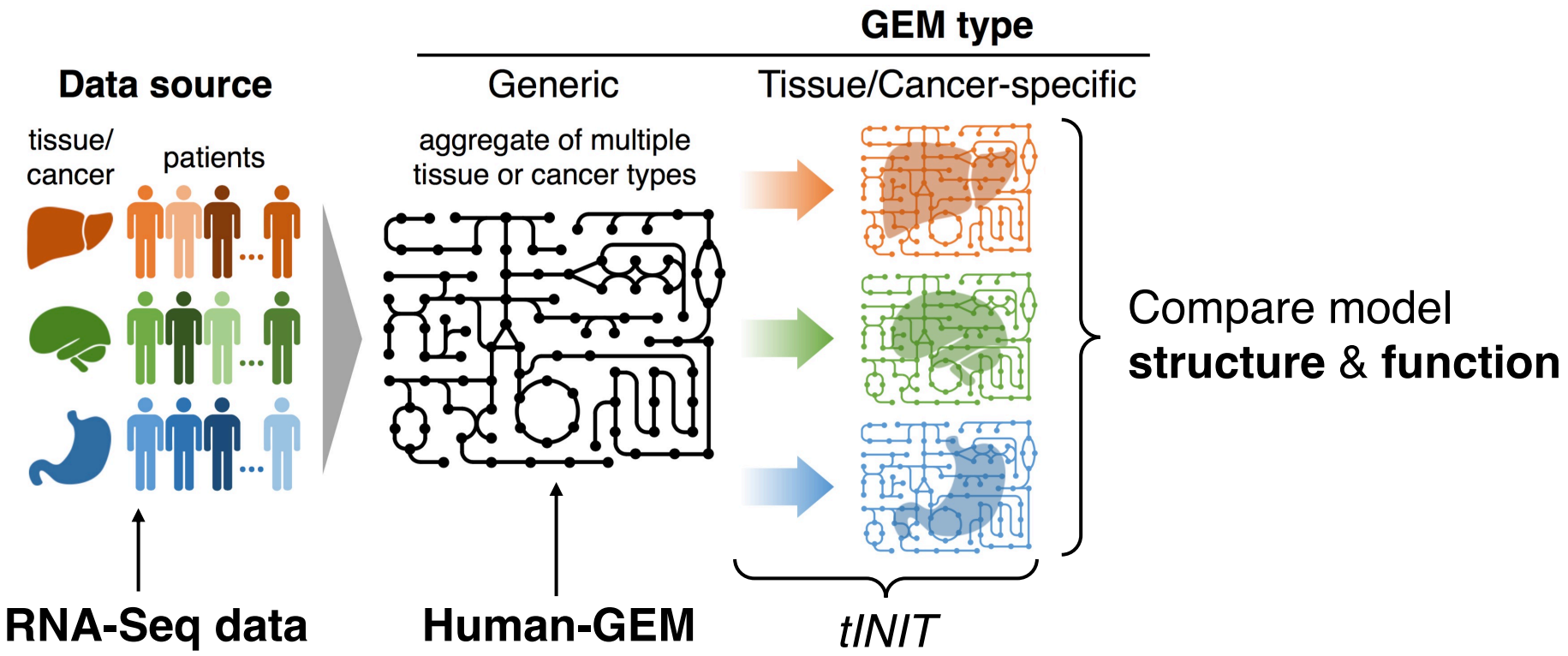






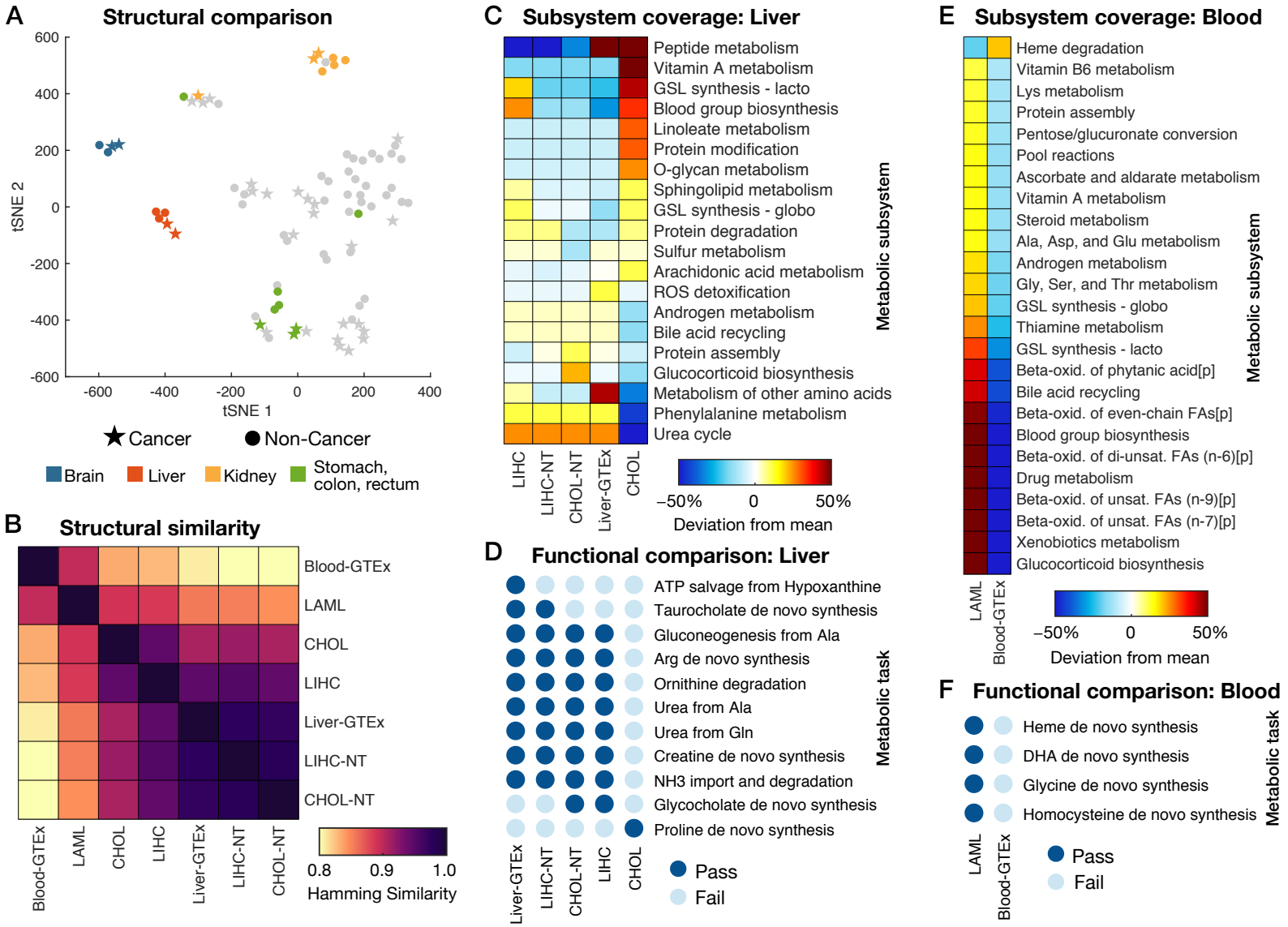
Generation of cell and tissue type GEMs (context-specific)

Context-specific GEMs enables investigating healthy and disease tissue differences *in the context of metabolism*



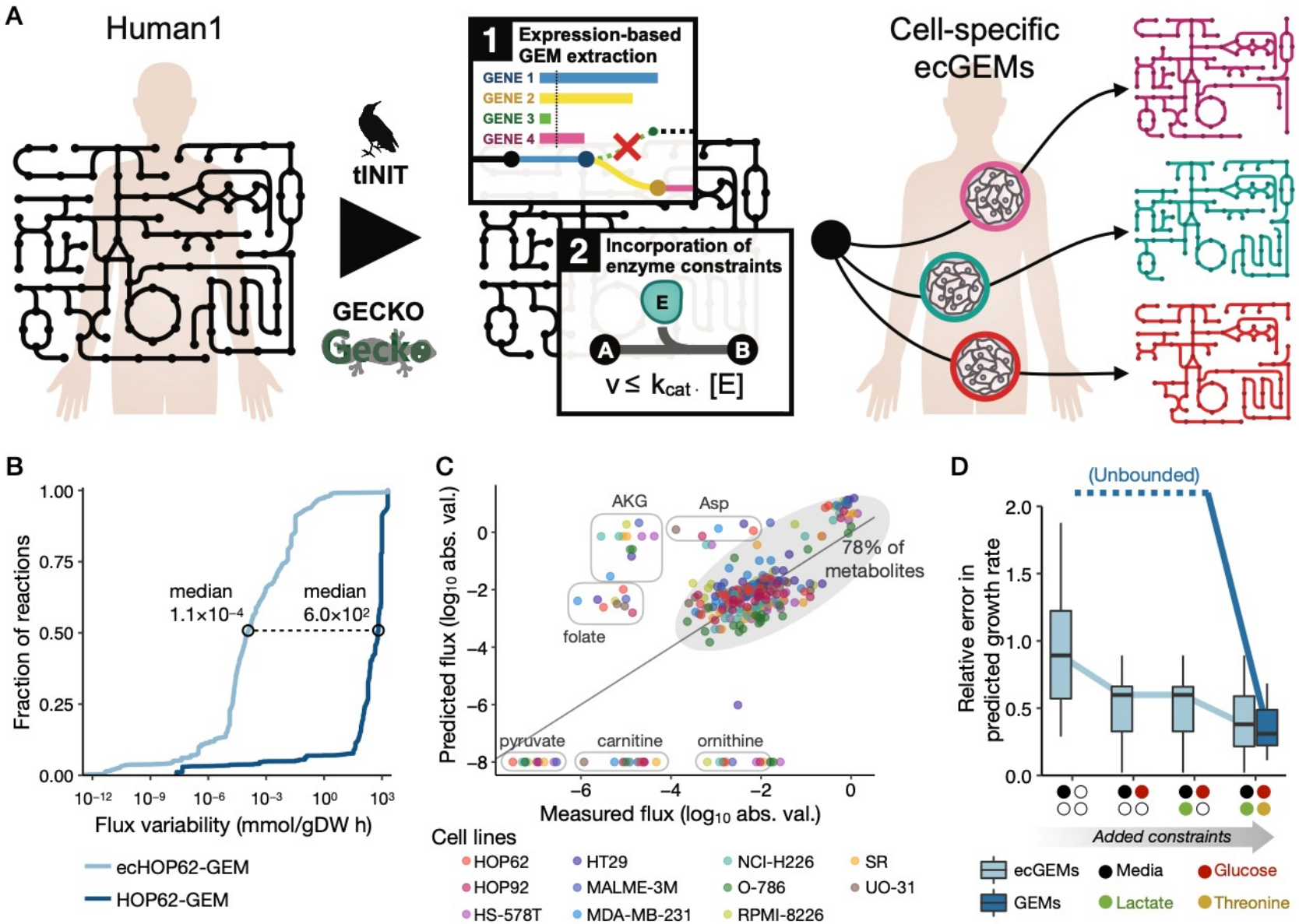
- TCGA
  - 33 tumor types
  - 23 paired-normal tissue types
- GTEx
  - 30 healthy tissue types

Structural and functional comparison of cancer- and healthy tissue–specific GEMs

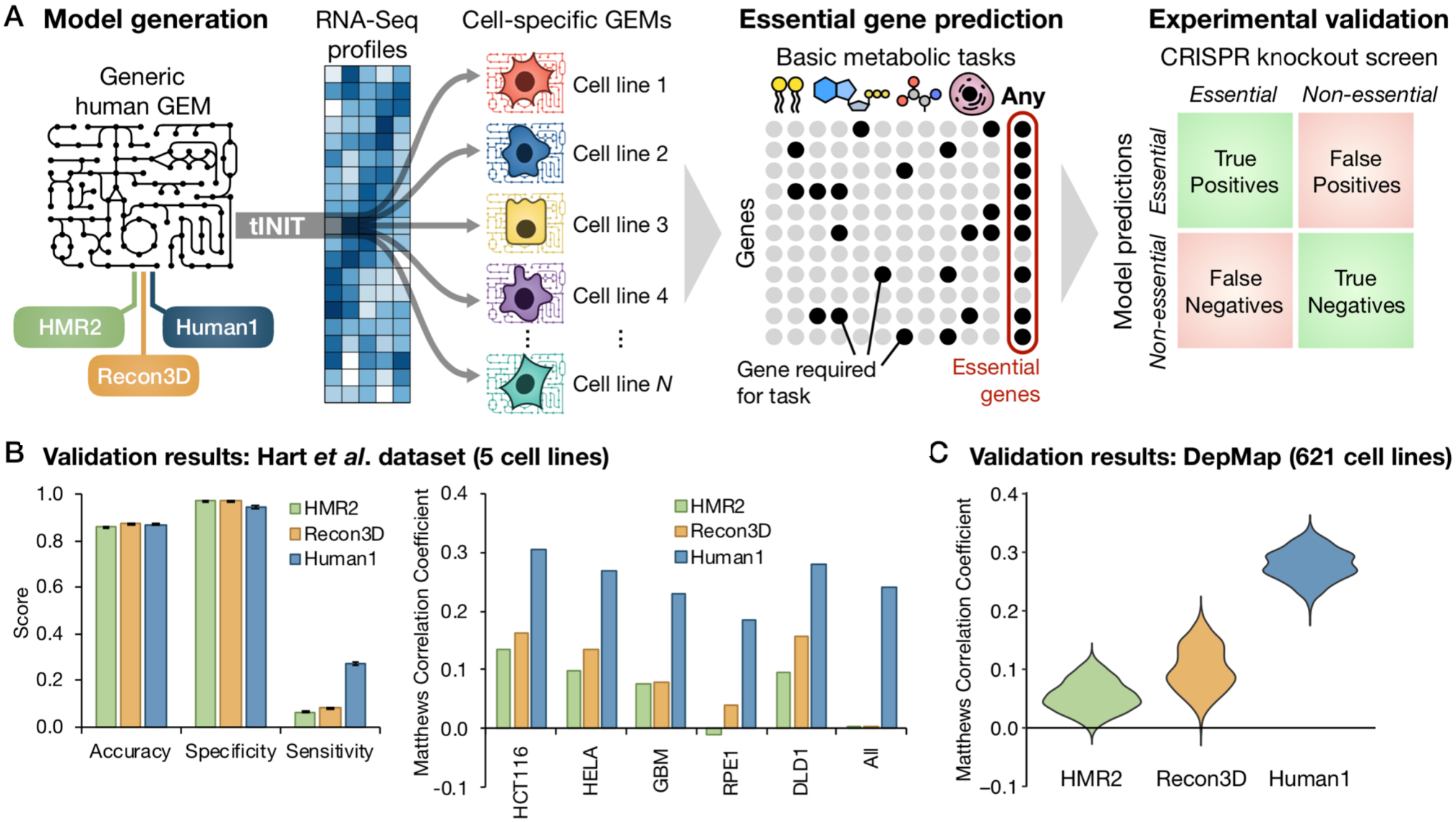


Science Signaling. 2020 13:eaaz1482

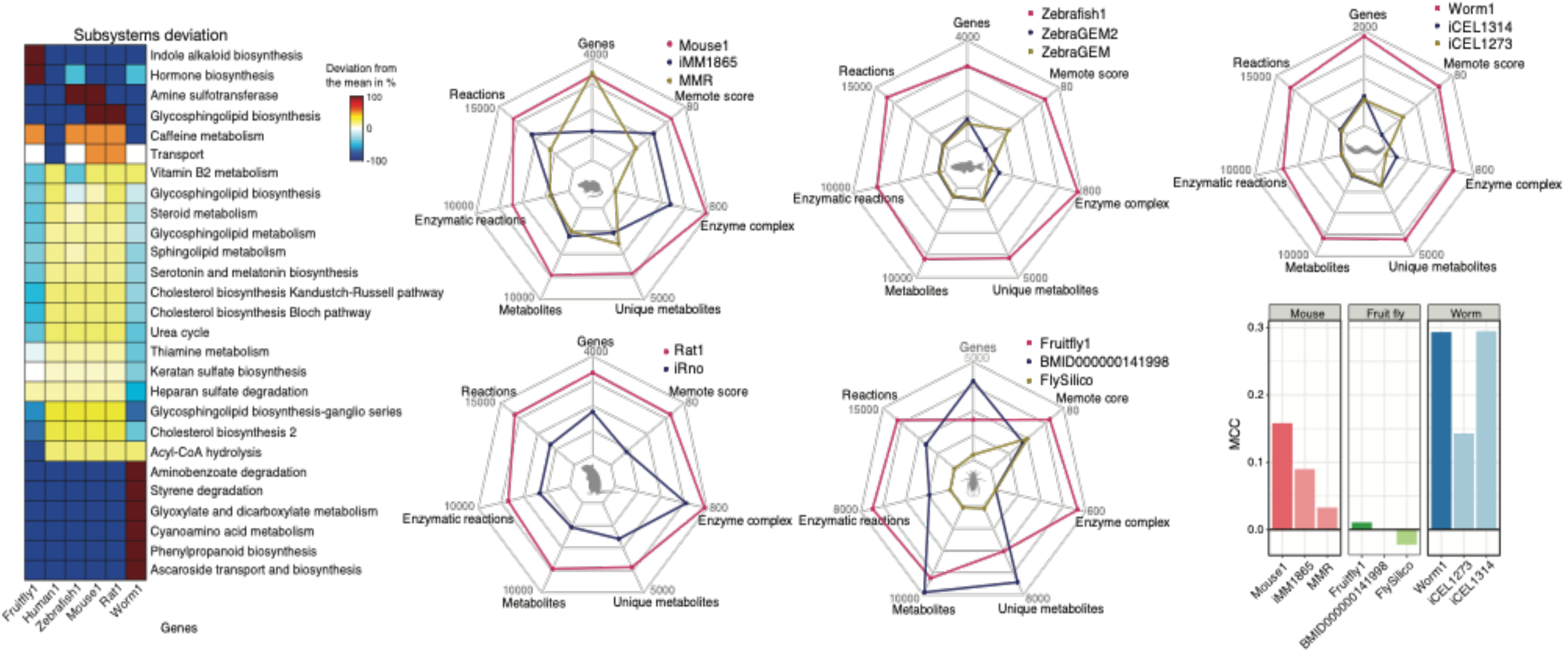
Generation and analysis of human cell-line ecGEMs



GEM validation using gene essentiality analysis



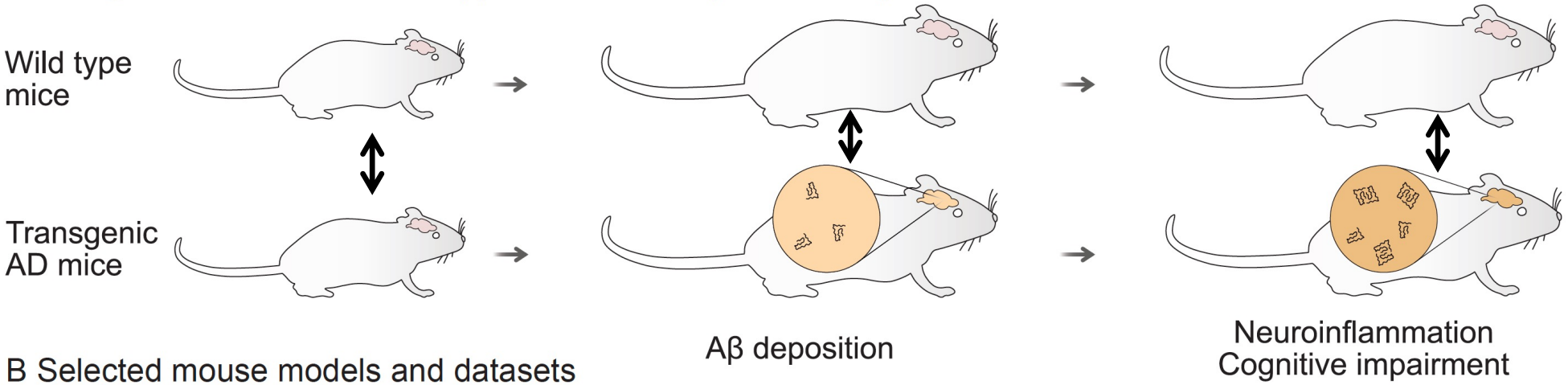
Comparison, evaluation, and validation of animal GEMs



PNAS. 2021 118:e2102344118

Studying AD mouse models using GEMs

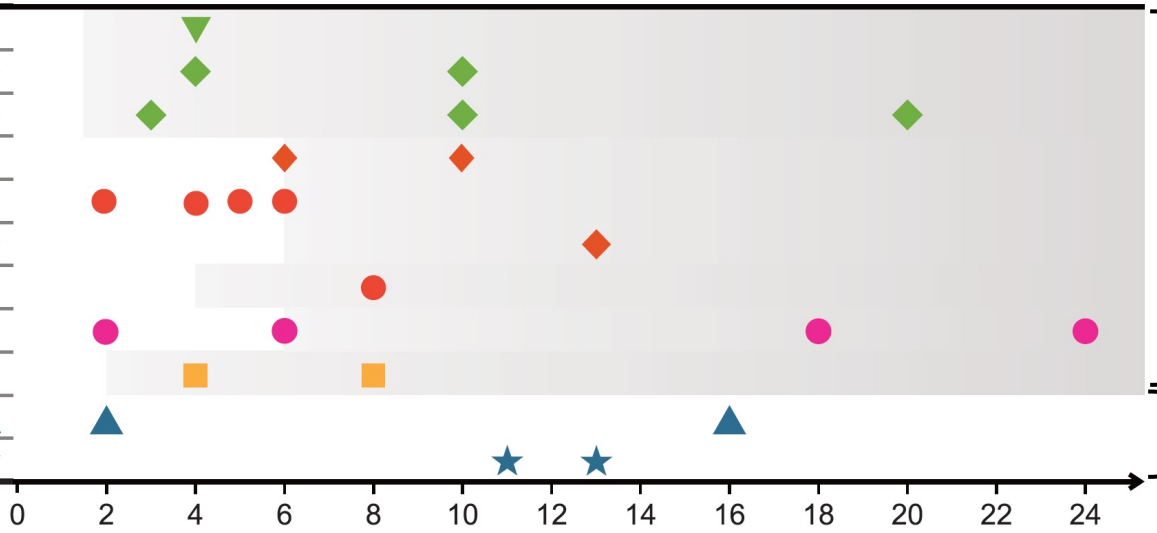
A Transgenic AD mice and wild type controls with paired time points



B Selected mouse models and datasets

AD mouse model	Dataset
APPPS1	GSE100070
	GSE110741
	GSE63943
APPswe/PSEN1dE9 (line 85)	GSE104424
	GSE136861
	GSE93678
APPswe/PSEN1dE9 (C57BL6)	GSE131659
APP23	GSE80465
Trem2 KO (KOMP) x APPPS1	GSE104381
Trem2 KO (JAX)	GSE134031
	GSE124266

Sample timepoints and Aβ deposition



with Aβ plaque deposition

without Aβ plaque deposition

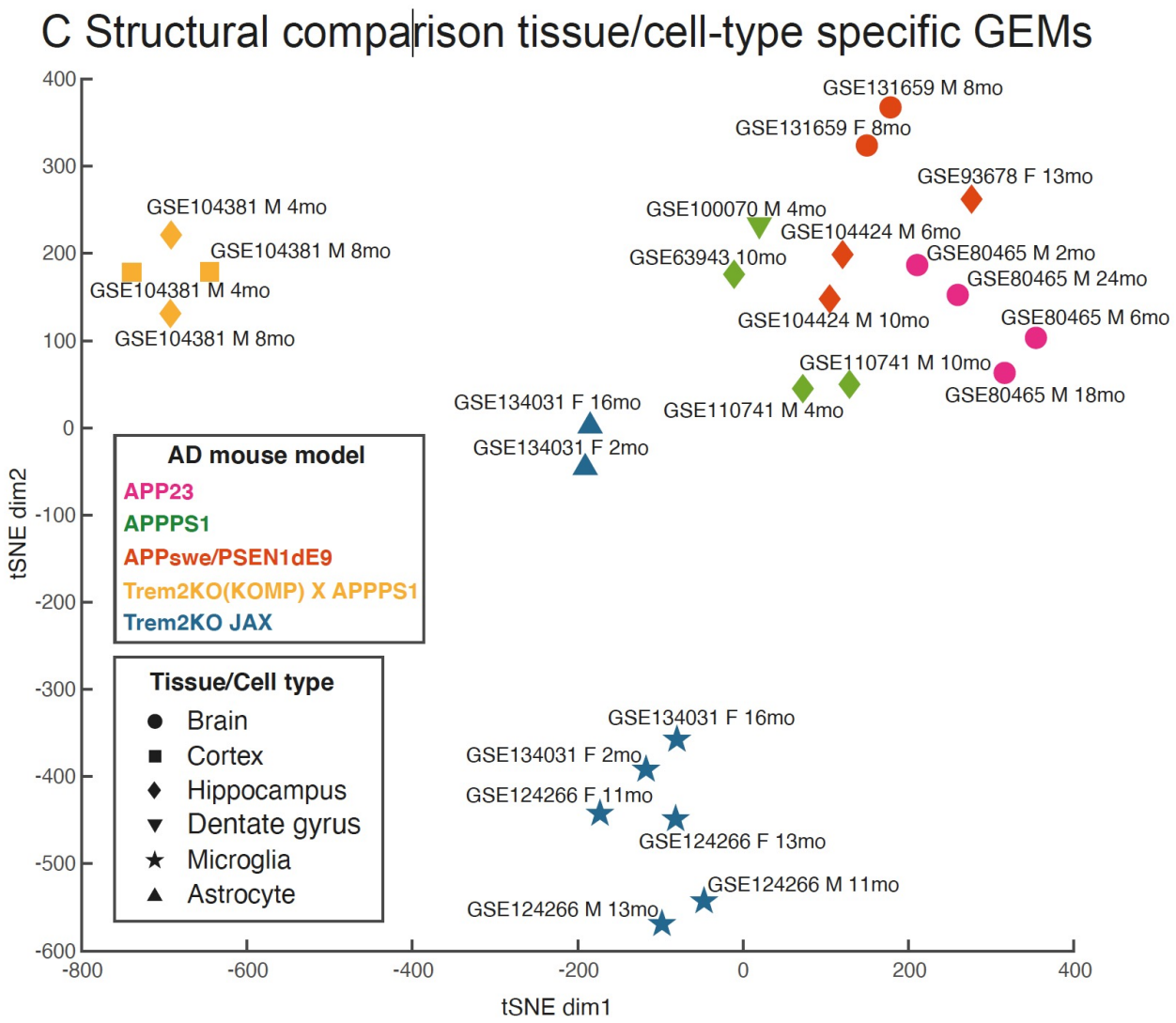
11 datasets

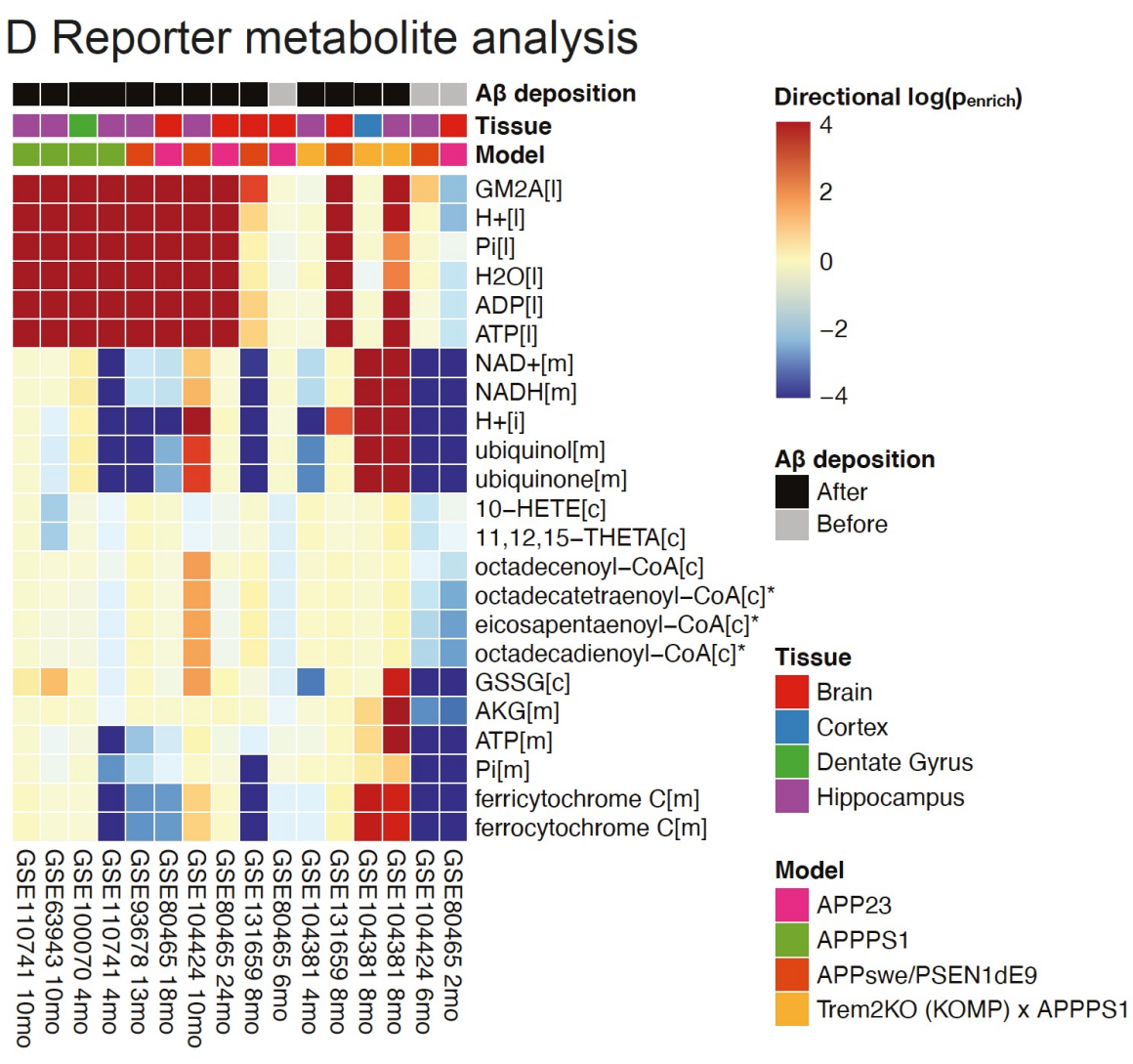
24 timepoints

54 conditions

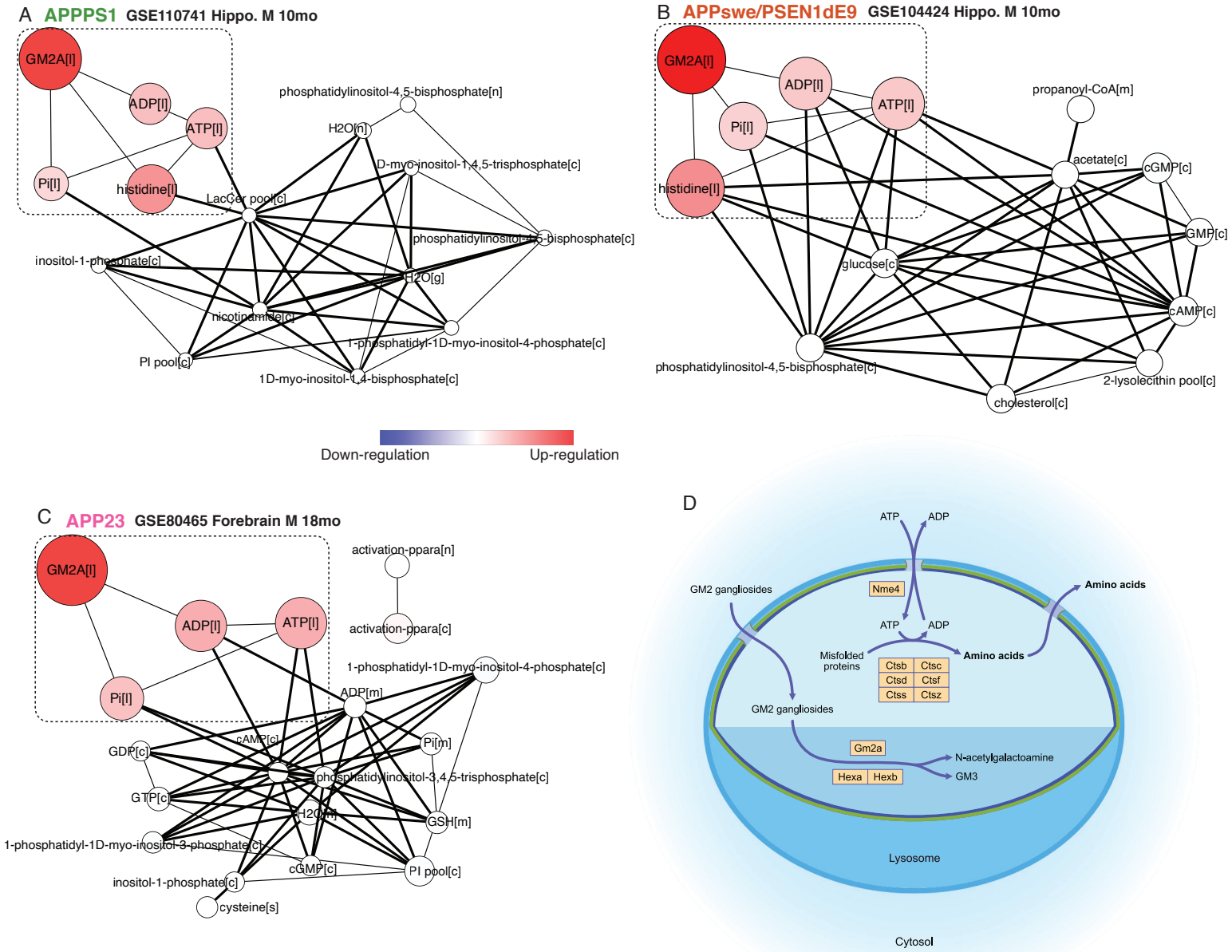
404 samples

Application of Mouse1 in studying AD mouse models

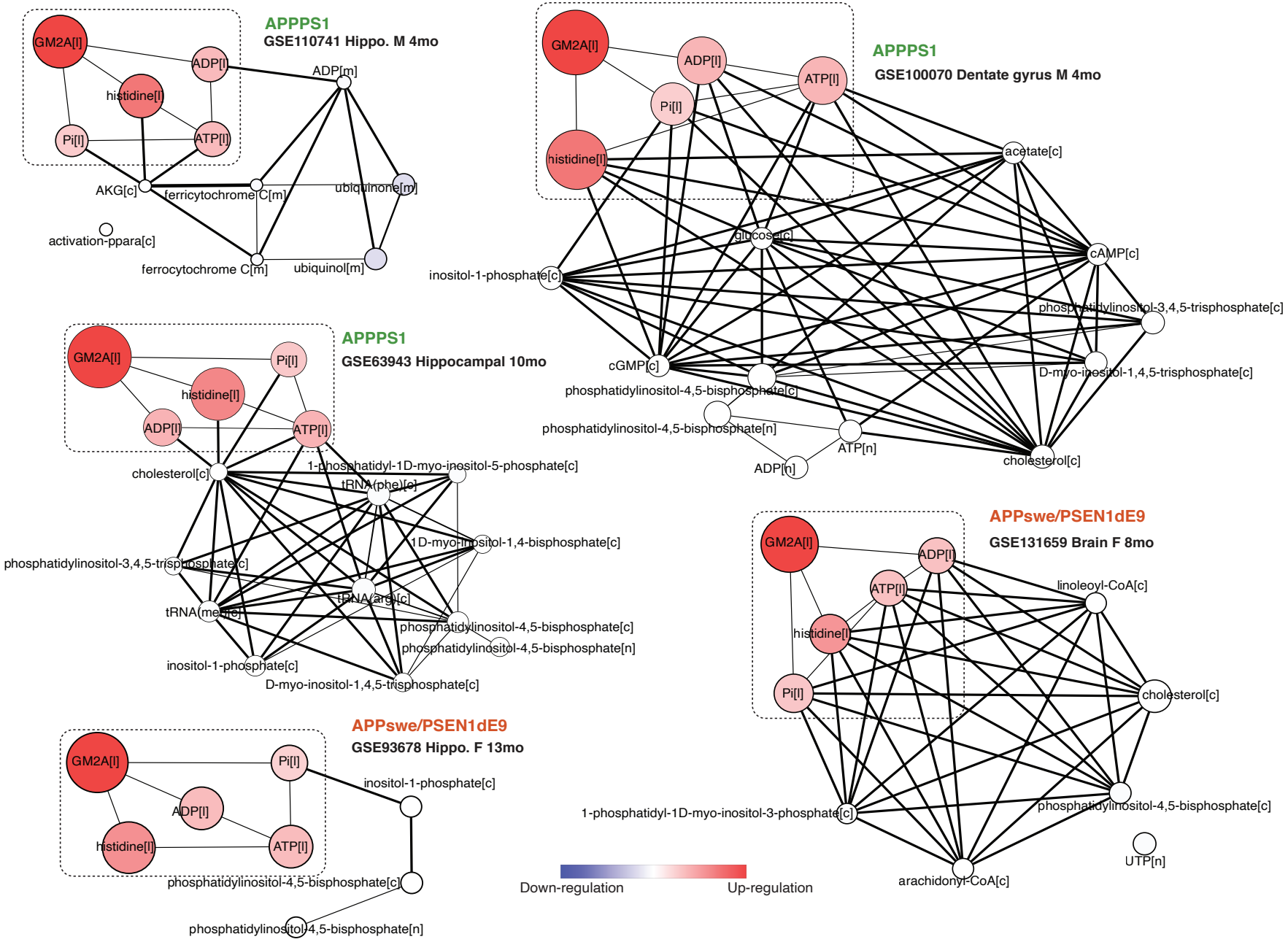


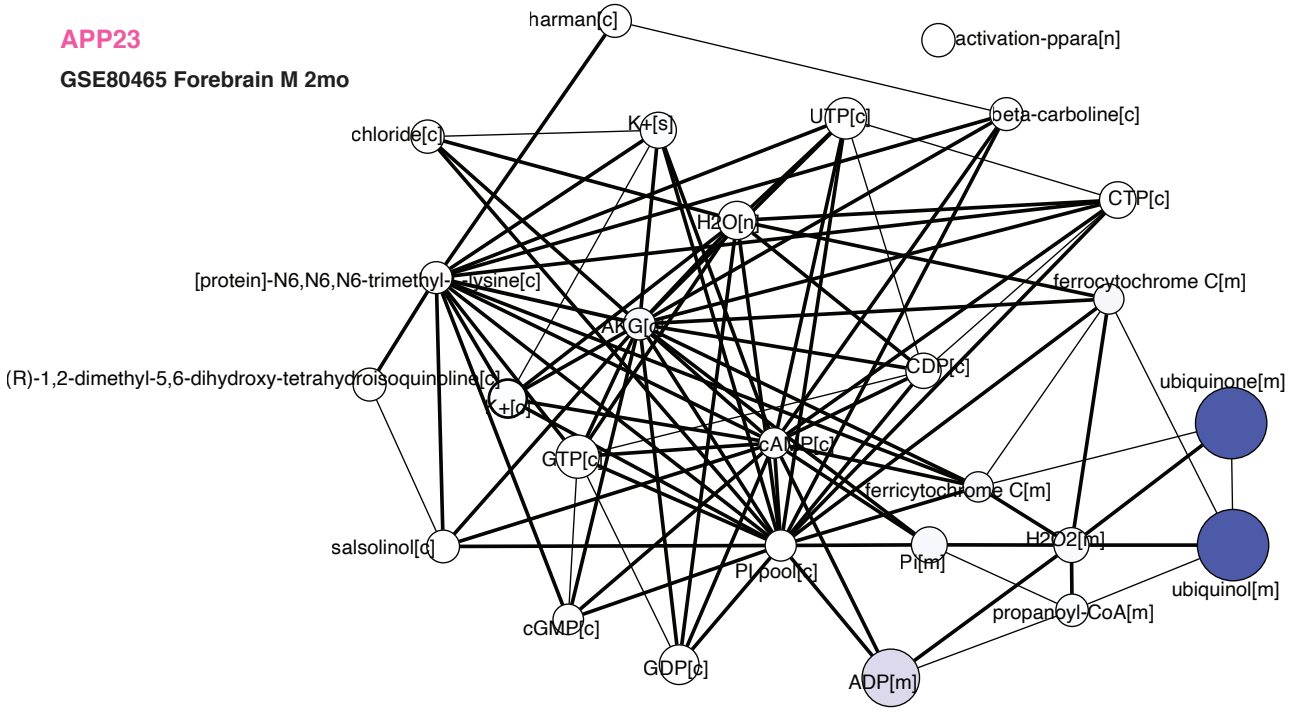


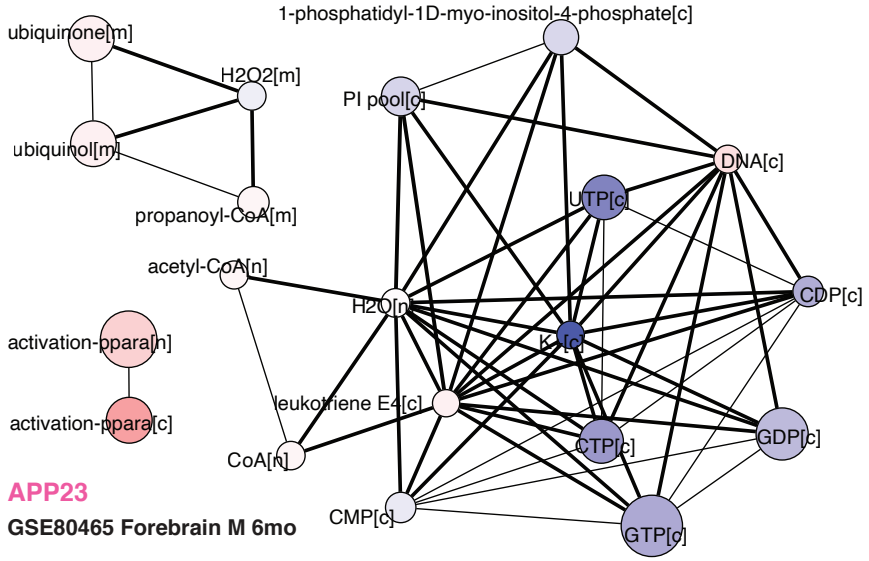
Integrative analysis of reporter metabolite gene sets with Mouse1

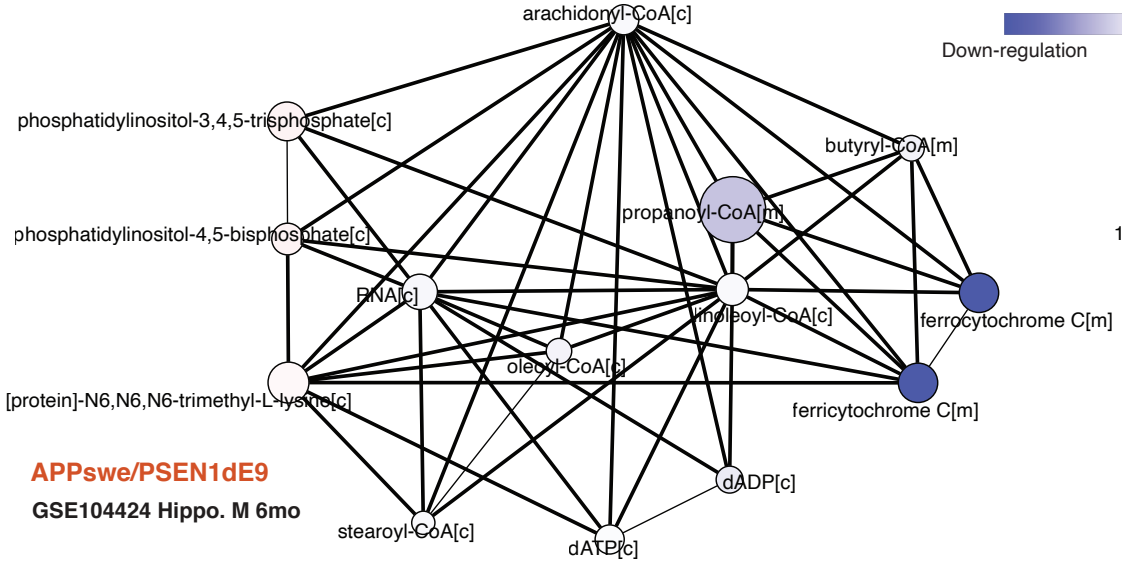


Upregulation of lysosomal activities is revealed by integrative analysis RNA-seq data from all three APP overexpression mouse models

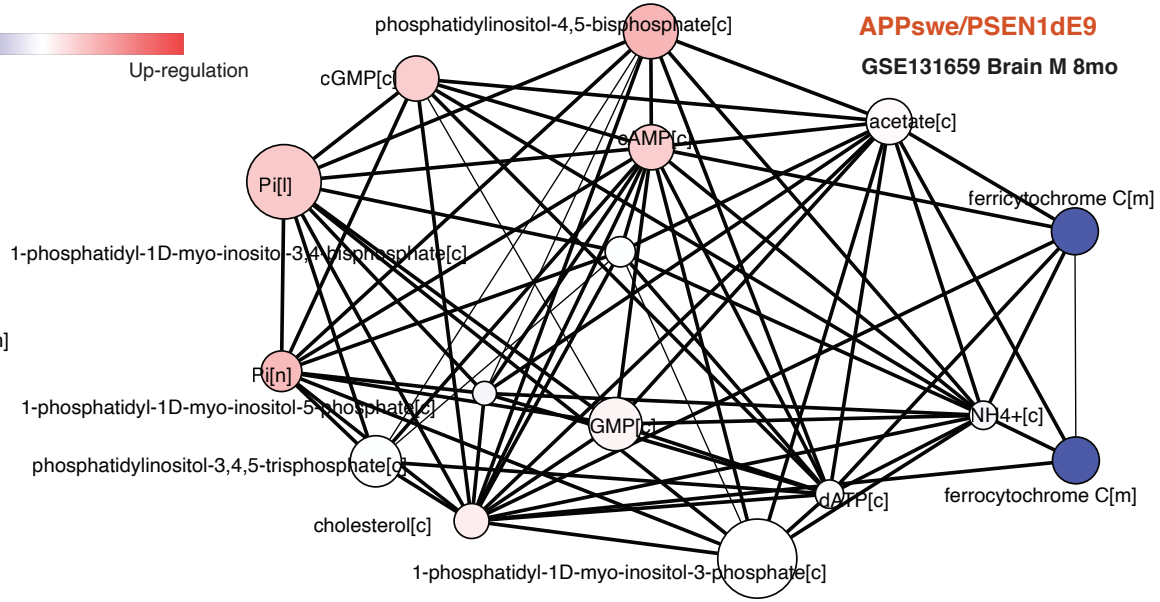

APPPS1
GSE110741 Hippo. M 4mo
GM2A[l]
ADP[l]
histidine[l]
Pi[l]
ATP[l]
ADP[m]
AKG[c]
ferricytochrome C[m]
ubiquinone[m]
activation-ppara[c]
ferrocytochrome C[m]
ubiquinol[m]
APPPS1
GSE100070 Dentate gyrus M 4mo
GM2A[l]
ADP[l]
ATP[l]
Pi[l]
histidine[l]
acetate[c]
glucose[c]
cAMP[c]
inositol-1-phosphate[c]
phosphatidylinositol-3,4,5-trisphosphate[c]
cGMP[c]
D-myo-inositol-1,4,5-trisphosphate[c]
phosphatidylinositol-4,5-bisphosphate[c]
phosphatidylinositol-4,5-bisphosphate[n]
ATP[n]
ADP[n]
cholesterol[c]
APPPS1
GSE63943 Hippocampal 10mo
GM2A[l]
Pi[l]
histidine[l]
ADP[l]
ATP[l]
cholesterol[c]
1-phosphatidyl-1D-myo-inositol-5-phosphate[c]
tRNA(phe)[c]
1D-myo-inositol-1,4-bisphosphate[c]
phosphatidylinositol-3,4,5-trisphosphate[c]
tRNA(arg)[c]
tRNA(met)[c]
phosphatidylinositol-4,5-bisphosphate[c]
phosphatidylinositol-4,5-bisphosphate[n]
inositol-1-phosphate[c]
D-myo-inositol-1,4,5-trisphosphate[c]
APPswe/PSEN1dE9
GSE131659 Brain F 8mo
GM2A[l]
ADP[l]
ATP[l]
linoleoyl-CoA[c]
histidine[l]
Pi[l]
cholesterol[c]
1-phosphatidyl-1D-myo-inositol-3-phosphate[c]
phosphatidylinositol-4,5-bisphosphate[c]
UTP[n]
arachidonyl-CoA[c]
APPswe/PSEN1dE9
GSE93678 Hippo. F 13mo
GM2A[l]
Pi[l]
inositol-1-phosphate[c]
ADP[l]
histidine[l]
ATP[l]
phosphatidylinositol-4,5-bisphosphate[c]
phosphatidylinositol-4,5-bisphosphate[n]
Down-regulation
Up-regulation


APP23
GSE80465 Forebrain M 2mo
harman[c]
activation-ppara[n]
chloride[c]
K+[s]
UTP[c]
beta-carboline[c]
CTP[c]
H2O[n]
[protein]-N6,N6,N6-trimethyl-L-lysine[c]
ferrocytochrome C[m]
AKG[c]
(R)-1,2-dimethyl-5,6-dihydroxy-tetrahydroisoquinoline[c]
CDP[c]
ubiquinone[m]
K+[c]
cAMP[c]
GTP[c]
ferricytochrome C[m]
salsolinol[c]
H2O2[m]
PI pool[c]
Pi[m]
ubiquinol[m]
propanoyl-CoA[m]
cGMP[c]
GDP[c]
ADP[m]

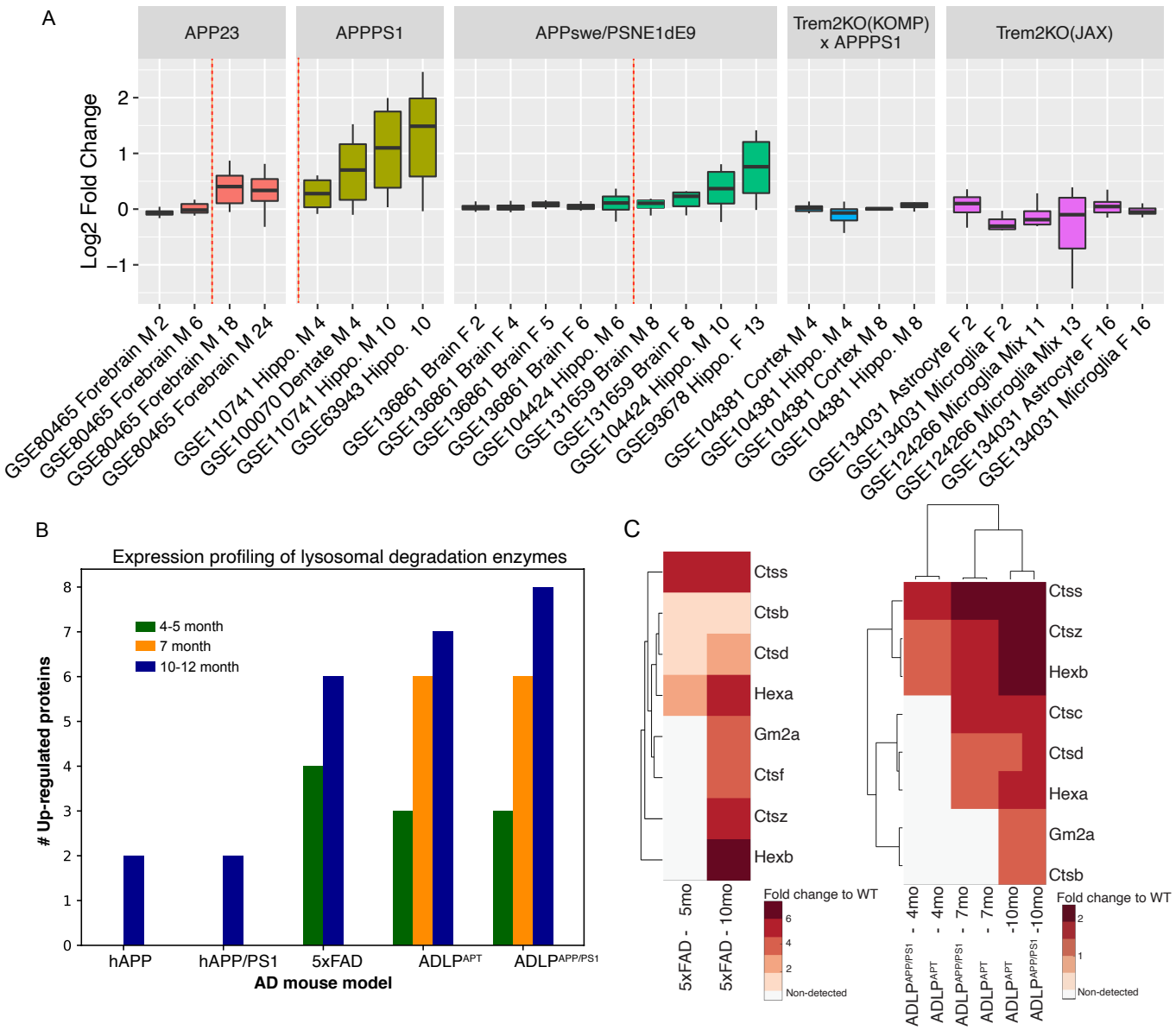

ubiquinone[m]
1-phosphatidyl-1D-myo-inositol-4-phosphate[c]
H2O2[m]
PI pool[c]
ubiquinol[m]
DNA[c]
UTP[c]
propanoyl-CoA[m]
acetyl-CoA[n]
CDP[c]
H2O[n]
activation-ppara[n]
K+[c]
leukotriene E4[c]
activation-ppara[c]
GDP[c]
CTP[c]
CoA[n]
APP23
GSE80465 Forebrain M 6mo
CMP[c]
GTP[c]


arachidonyl-CoA[c]
phosphatidylinositol-3,4,5-trisphosphate[c]
butyryl-CoA[m]
propanoyl-CoA[m]
phosphatidylinositol-4,5-bisphosphate[c]
RNA[c]
linoleoyl-CoA[c]
ferrocytochrome C[m]
oleoyl-CoA[c]
[protein]-N6,N6,N6-trimethyl-L-lysine[c]
ferricytochrome C[m]
APPswe/PSEN1dE9
GSE104424 Hippo. M 6mo
dADP[c]
stearoyl-CoA[c]
dATP[c]

Down-regulation
Up-regulation


phosphatidylinositol-4,5-bisphosphate[c]
APPswe/PSEN1dE9
GSE131659 Brain M 8mo
cGMP[c]
acetate[c]
cAMP[c]
Pi[l]
ferricytochrome C[m]
1-phosphatidyl-1D-myo-inositol-3,4-bisphosphate[c]
Pi[n]
1-phosphatidyl-1D-myo-inositol-5-phosphate[c]
GMP[c]
NH4+[c]
phosphatidylinositol-3,4,5-trisphosphate[c]
dATP[c]
ferrocytochrome C[m]
cholesterol[c]
1-phosphatidyl-1D-myo-inositol-3-phosphate[c]

Validation of upregulated lysosomal degradation pathways



(A) Box plot shows the log2 fold changes (AD versus control) of the 10 genes (***Gm2a***, ***Hexa***, ***Hexb***, ***Ctsb***, ***Ctsc***, ***Ctsd***, ***Ctsf***, ***Ctss***, ***Ctsz***, ***Nme4***) involved in GM2 ganglioside and peptide degradation. The samples from each mouse model are order by time and the onset of Aβ deposition in APP overexpression models are indicated by dashed red lines.

(B) Bar plot shows the number of significantly ($p < 0.05$) upregulated lysosomal degradation proteins (out of 10) between AD and control at different time points in another 5 APP overexpression models.

(C) Heatmaps show the fold changes of the lysosomal digestive enzymes at different time points from APP overexpression models: 5xFAD, ADLP^{APPPS1} and ADLP^{APT}

Validation using human CSF samples

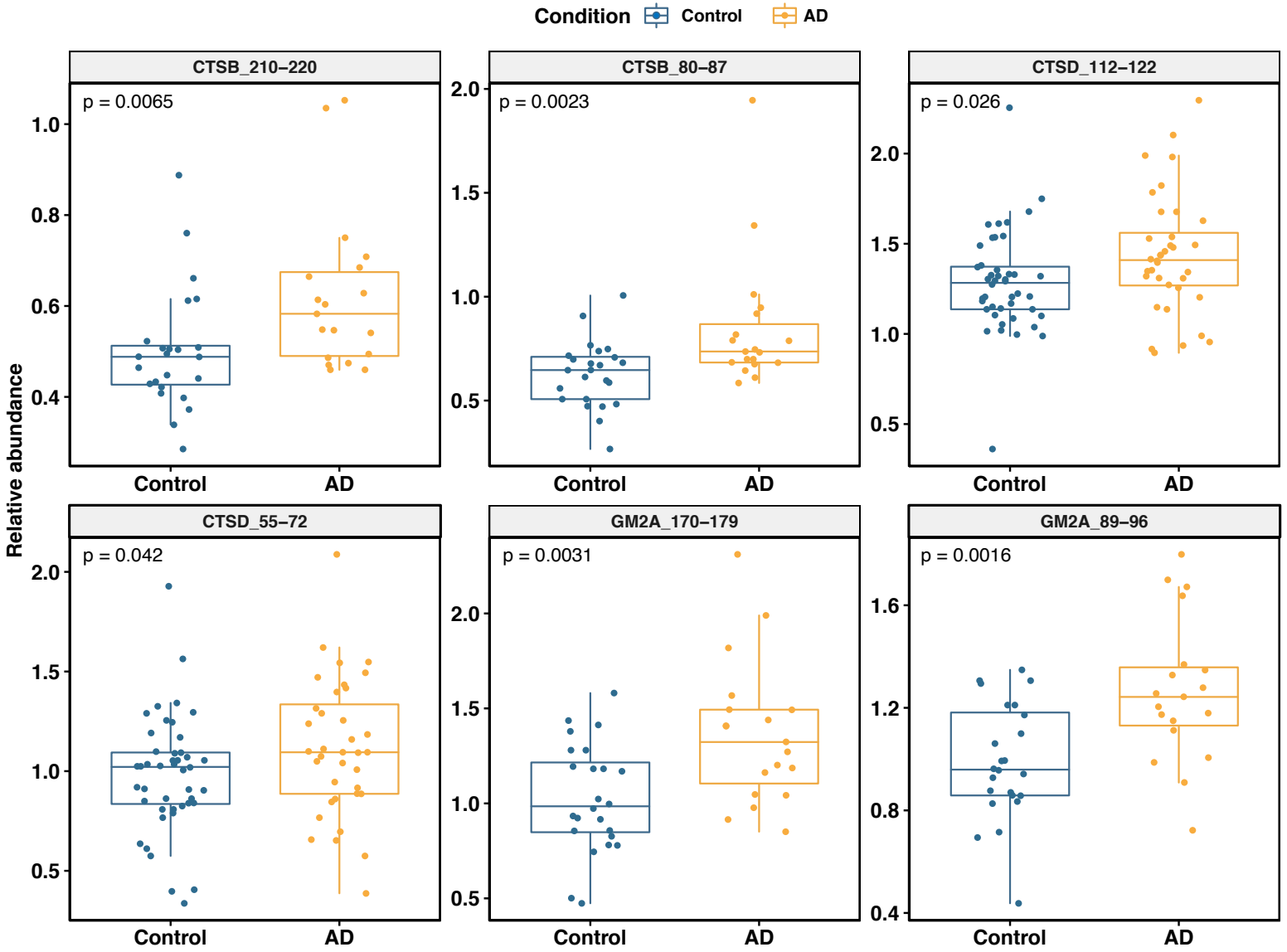
6 out of 17 lysosomal peptides were detected as significantly over-expressed in AD patient CSF samples, compared to those in CSF samples of healthy control.

AD (19) vs. Control (24)

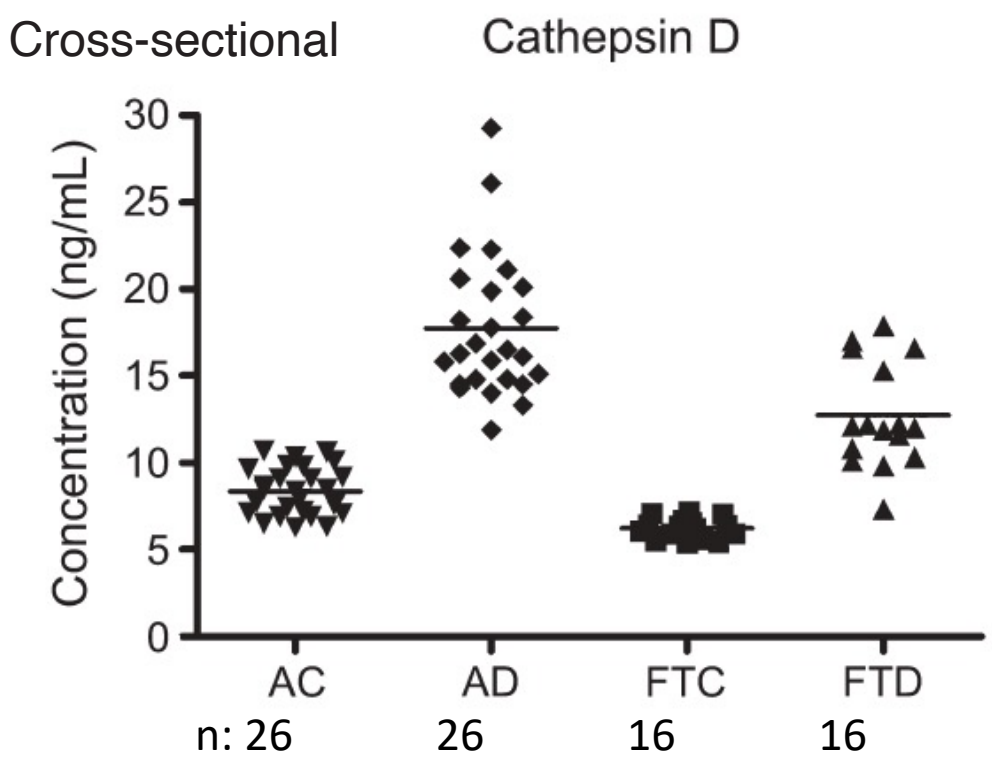
Peptides from the pilot study:
CTSB_80-87
CTSB_210-220
GM2A_89-96
GM2A_170-179

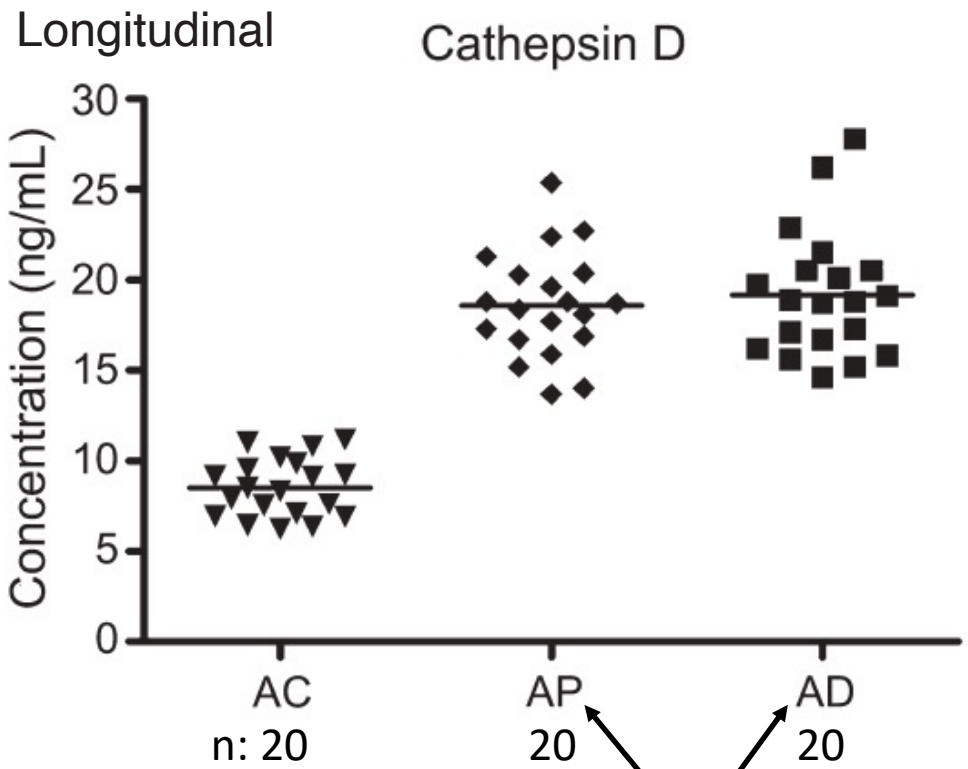
AD (36) vs. Control (44)

Peptides from clinical study II:
CTSD_55-72
CTSD_112-122



ELISA quantification showed elevated CstD in blood samples of AD patients





AC, Normal control; **AD**, Alzheimer disease;
FTC, frontotemporal normal control;
FTD, frontotemporal dementia;
AP, preclinical AD

Measured from the same patients both in AP (preclinical AD) and AD stages, with intervals either in 1 to 5 years (n=7) or 6 to 10 years (n=13).

Neurology. 2015 85(1):40-7.

Explore the integrated models

1. Select a model:

Fruitfly-GEM 1.1.0
Drosophila melanogaster
12072 reactions - 8164 metabolites - 2048 genes

Human-GEM 1.8.0
Homo sapiens
13417 reactions - 4164 metabolites - 3625 genes

Mouse-GEM 1.2.0
Mus musculus
13094 reactions - 8404 metabolites - 3510 genes

Rat-GEM 1.2.0
Rattus norvegicus
13102 reactions - 8408 metabolites - 3499 genes

Worm-GEM 1.1.0
Caenorhabditis elegans
12169 reactions - 8158 metabolites - 1946 genes

Yeast-GEM 8.4.2
Saccharomyces cerevisiae
3991 reactions - 1331 metabolites - 1149 genes

Zebrafish-GEM 1.1.0
Danio rerio
12956 reactions - 8384 metabolites - 3228 genes

https://metabolicatlas.org/

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Comments and questions?