Identifying proteins and metabolic pathways associated to the neuroprotective response mediated by tibolone in astrocytes under an induced inflammatory model

Daniel Osorio[1,2,3] **Janneth Gonzalez**[2] **Andrés Pinzon**[3]

[1]Departamento de Ingeniería de Sistemas e Industrial
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Instituto de Genética, Universidad Nacional de Colombia

Universidad Nacional de Colombia, November 2016

Neuroinflammation

Neurodegenerative diseases | Cardiovascular events | Stress

Smoke | Obesity (Over Nutrition or Caloric Excess)

Metabolic Inflammation or Metainflammation

▼ Leptine + ▼ Insuline → ▲ IKKβ + ▲ NF$\kappa\beta$

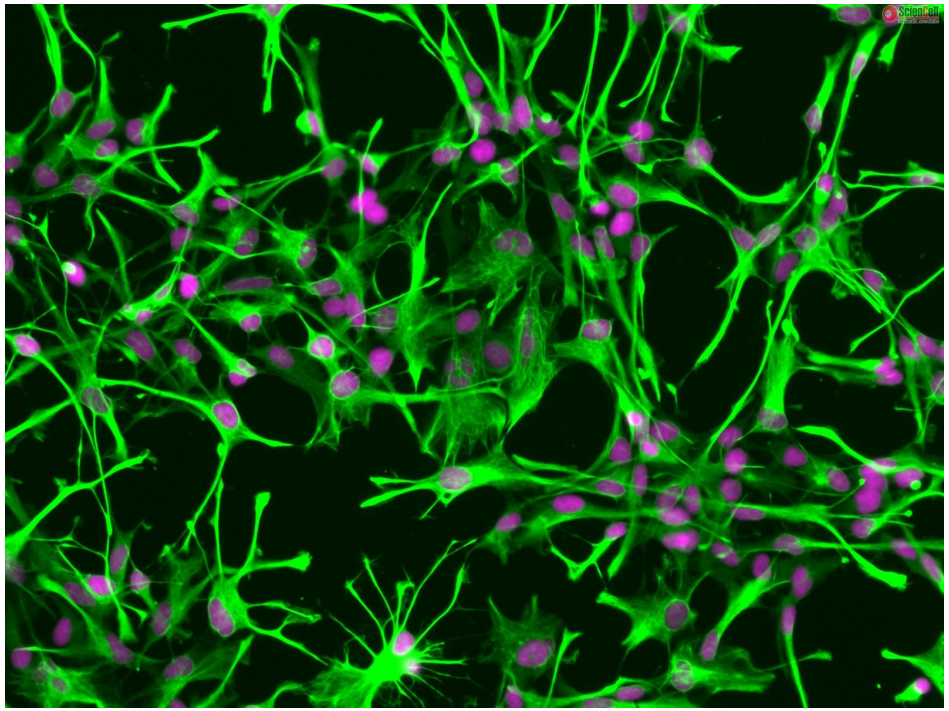
Metabolic Inflammation or Metainflammation

▼ Leptine + ▼ Insuline → ▲ IKKβ + ▲ NF$\kappa\beta$

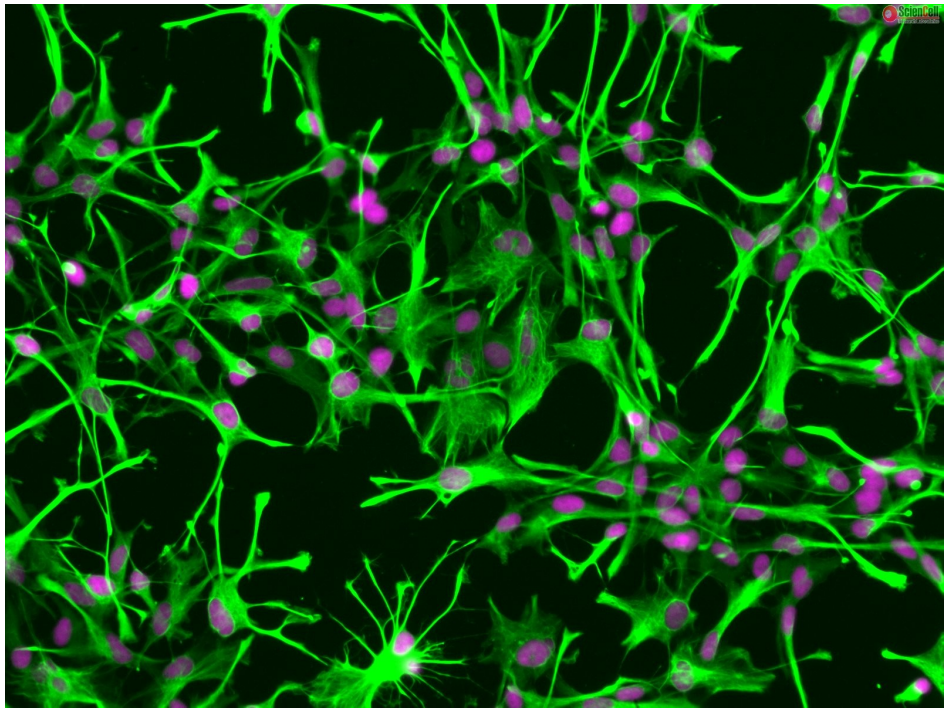
▲ Endoplasmic reticulum stress → ▲ UPR

▲ Reactive C Protein Ligands + ▲ TNFα + ▲ IL6 + ▲ ROS

Astrocytes Metabolic Functions

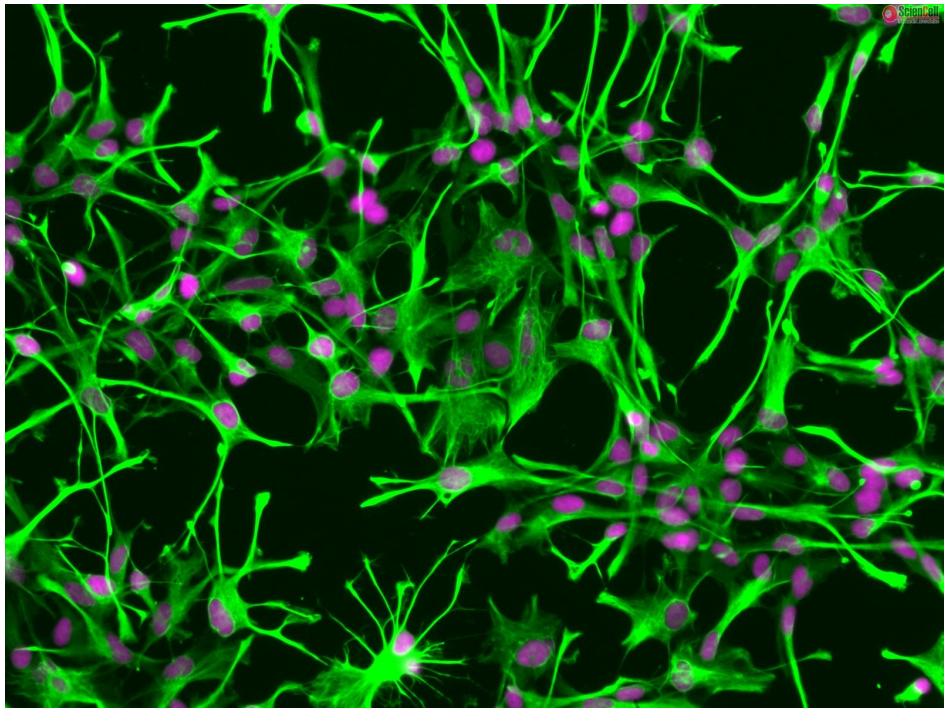


Astrocytes Metabolic Functions



K^+ Membrane Potential

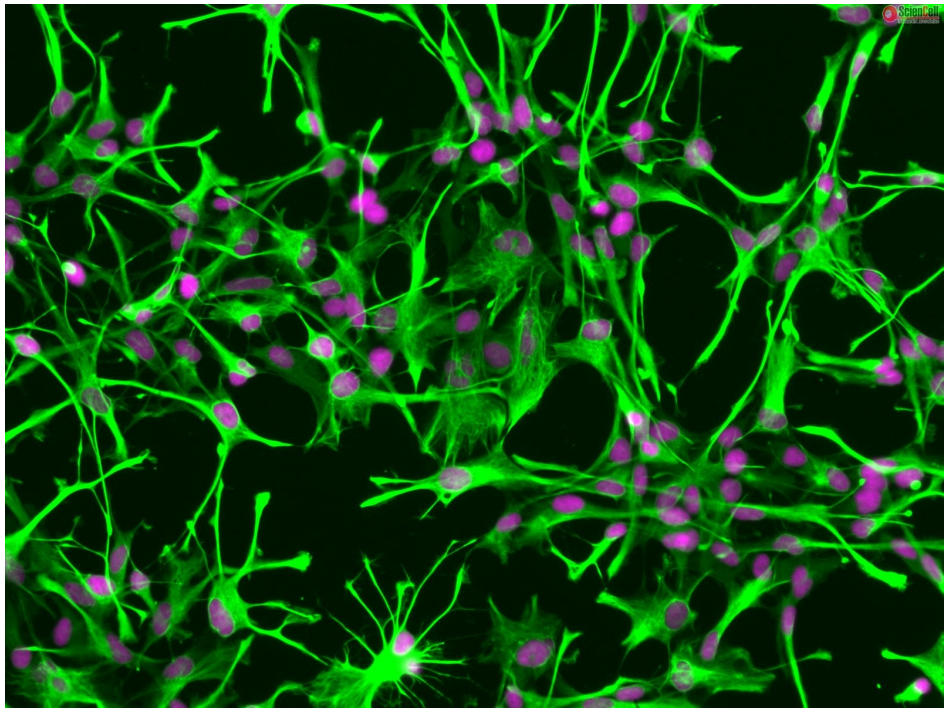
Astrocytes Metabolic Functions



K^+ Membrane Potential

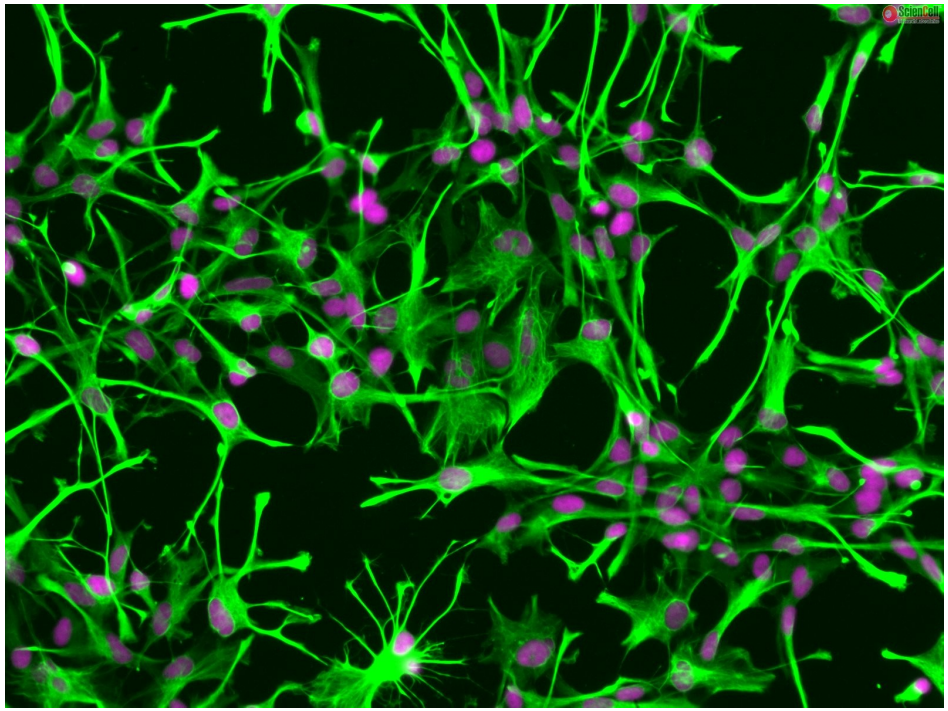
Ca^{+2} signaling

Astrocytes Metabolic Functions



K^+ Membrane Potential | Ca^{+2} signaling | Lactate release

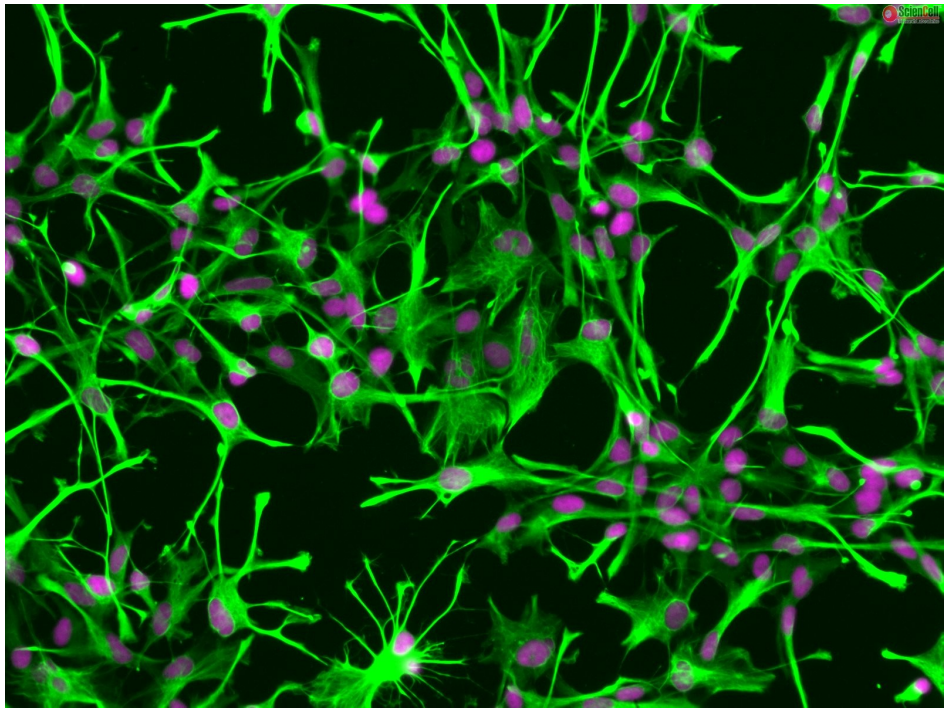
Astrocytes Metabolic Functions



K^+ Membrane Potential | Ca^{+2} signaling | Lactate release

[Dopa], [Glu], [GABA], [Gly] and [Cys] regulator

Astrocytes Metabolic Functions



K^+ Membrane Potential

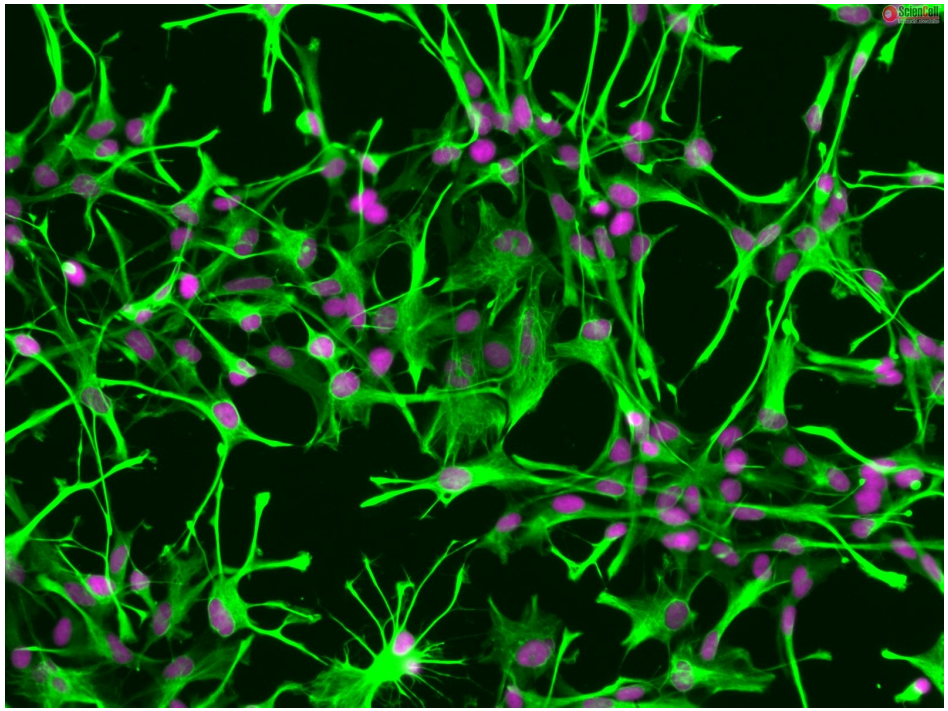
Ca^{+2} signaling

Lactate release

[Dopa], [Glu], [GABA], [Gly] and [Cys] regulator

pH maintenance

Astrocytes Metabolic Functions



K^+ Membrane Potential | Ca^{+2} signaling | Lactate release

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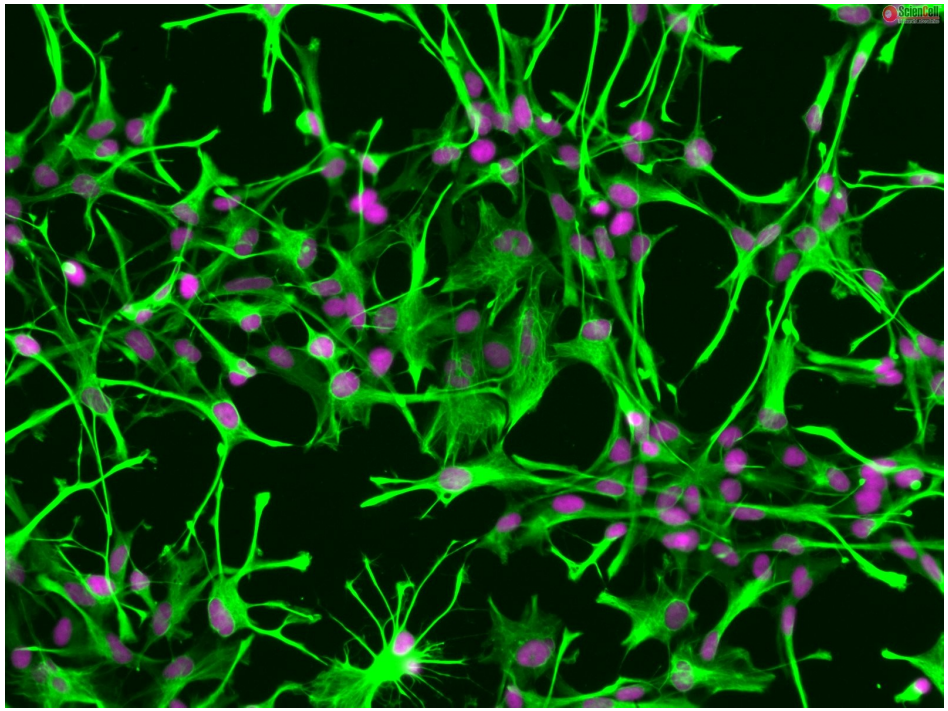
pH maintenance | ROS detox

Astrocytes Metabolic Functions



K^+ Membrane Potential | Ca^{+2} signaling | Lactate release

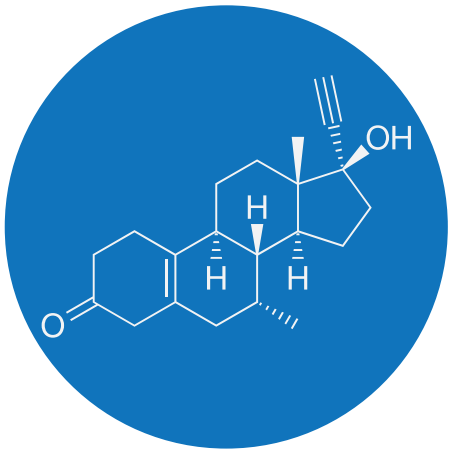
[Dopa], [Glu], [GABA], [Gly] and [Cys] regulator

pH maintenance | ROS detox | Gln, ATP and D-serine release

What effects does tibolone have on Astrocytic inflammatory scenarios?

Tibolone protects astrocytic cells from glucose deprivation through a mechanism involving estrogen receptor beta and the upregulation of neuroglobin expression

Marco Avila-Rodriguez [a, c], Luis Miguel Garcia-Segura [b, **], Oscar Hidalgo-lanussa [a], Eliana Baez [a], Janneth Gonzalez [a], George E. Barreto [a, d, e, *]



Objectives:

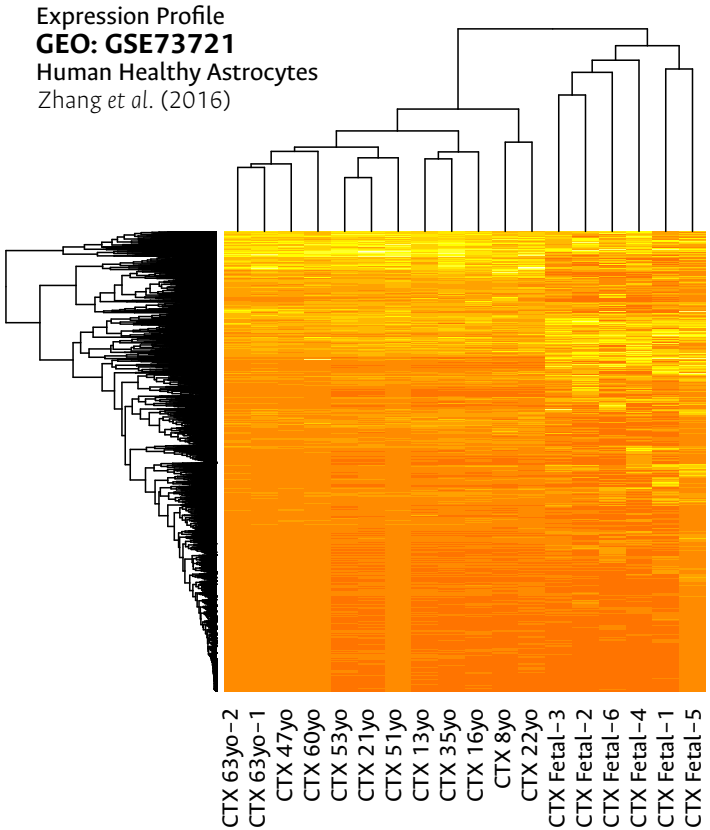
To identify proteins and metabolic pathways involved in the neuroprotective effects of tibolone in human astrocytes based in metabolic scenarios comparation we set:

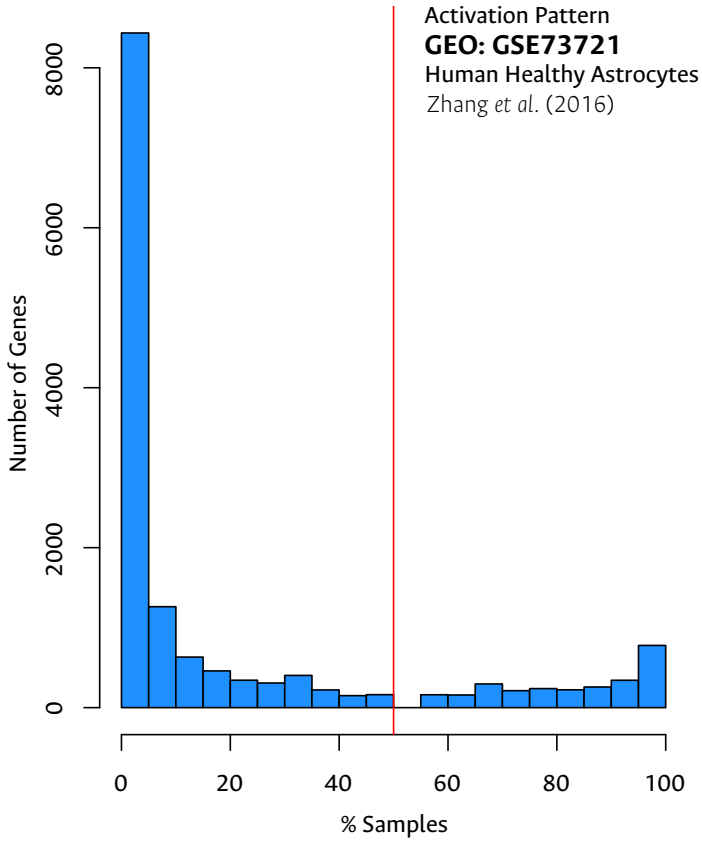
- Build a tissue specific computational model of astrocytes metabolism using gene expression data integration.
- Evaluate the effects caused by the increase of free fatty acids and tibolone presence in astrocytes metabolism.
- Determine metabolic pathways and relevant functional products in response to steroid tibolone through systems biology approximations.
- Evaluate the importance of proteins and metabolic pathways previously identified on the dynamics of the metabolic model.

OBJECTIVE 1:

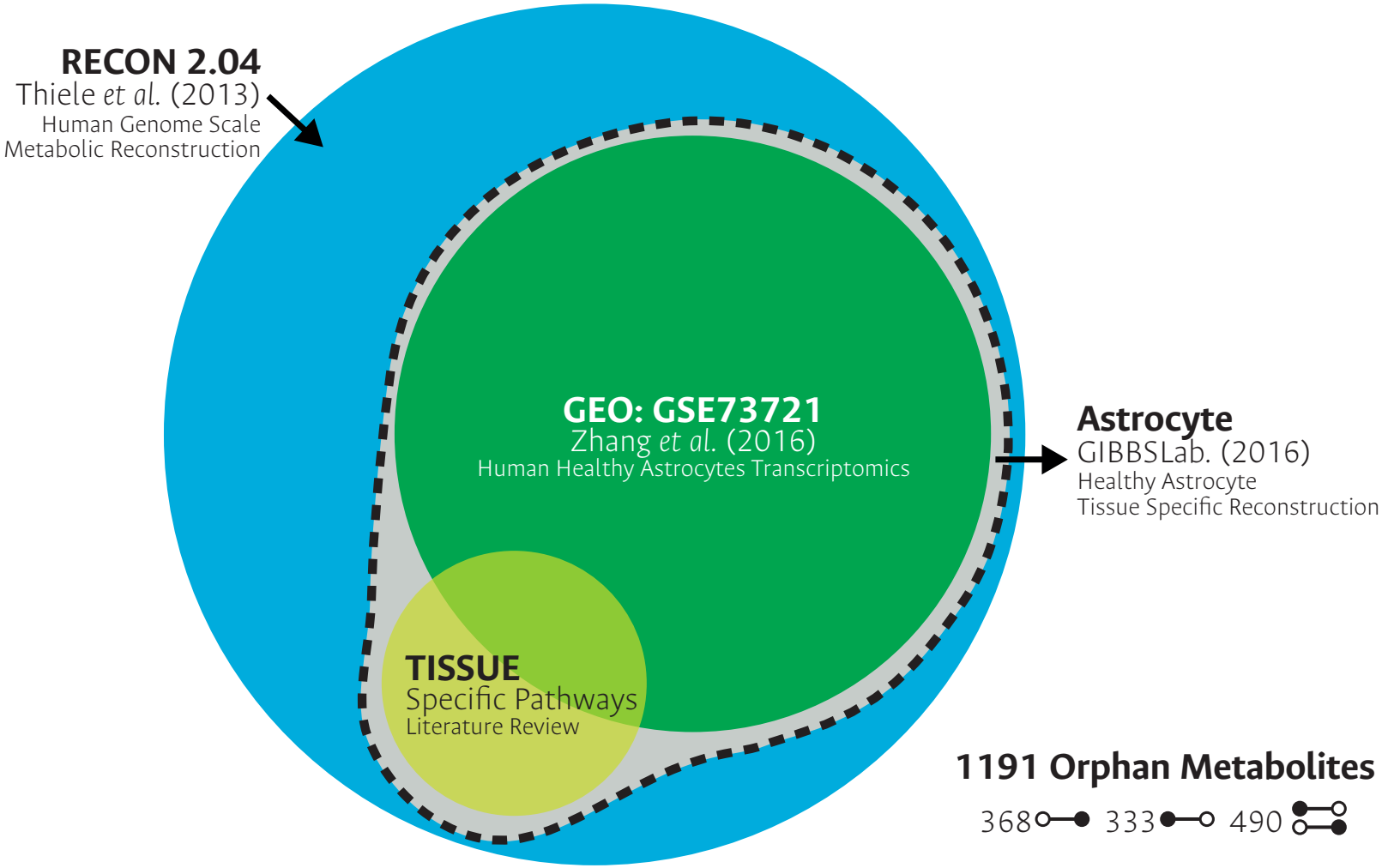
Build a tissue specific computational model of astrocytes metabolism using gene expression data integration.

Human Astrocytes Gene Expression Data





Mapping Reactions



Software Development

'g2f' Package

An R Package to Find and Fill Gaps for genome-scale metabolic networks

*Kelly Botero, **Daniel Osorio**, Janneth Gonzalez and Andres Pinzón-Velasco.*

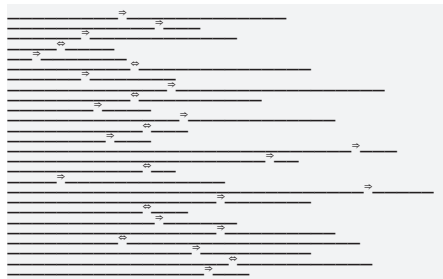
Language: R
Stable: CRAN
Development: gibbslab/g2f
License: GPL-2
Binaries: Windows - Linux - Mac

RXNLIST

h2o[r] + dheas[r] ⇒ h[r] + dhea[r] + so4[r]
uri[e] ⇔ uri[c]
na1[e] + uri[e] ⇒ na1[c] + uri[c]
atp[c] + pi[m] ⇒ pi[c] + atp[m]
na1[e] + gchola[e] ⇒ na1[c] + gchola[c]
...

getReference( )
DOWNLOAD STOICHIOMETRIC REACTIONS FROM THE KEGG DATABASE

REFERENCE



GENOME SCALE METABOLIC NETWORK

additionCost( )
CALCULATE ADITION COST

$$cost = \frac{n(metabolites(newReaction) \notin metabolites(reactionList))}{n(metabolites(newReaction))}$$

gapFill( )
FIND AND FILL GAPS

```
original = n( orphanMetabolites )
do{
    if(orphanMetabolite ∈ metabolites(newReactions)){
        gapFill: cost ⩽ limit → reaction ∪ newReactions
                 cost ⩾ limit → reaction
    }
    filled = n(orphans(reaction ∪ newReactions) ∈ orphanMetabolites)
}
while ( original ⩽ filled )
```

blockedReactions( )
IDENTIFY REACTIONS NEVER ACTIVATED

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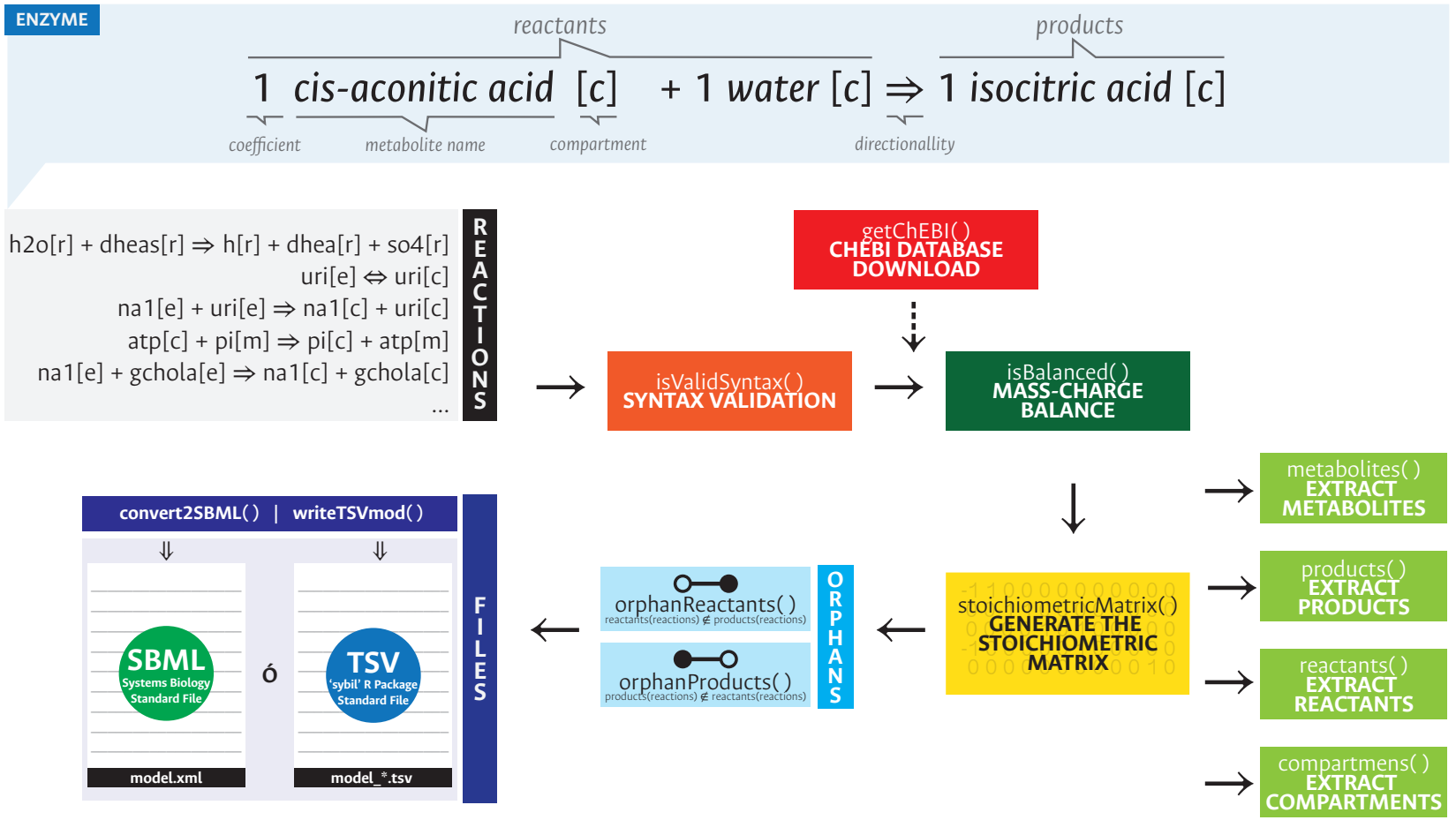

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An R Package to convert expression data to FBA fluxes

Daniel Osorio, Kelly Botero, Janneth Gonzalez and Andres Pinzón-Velasco.

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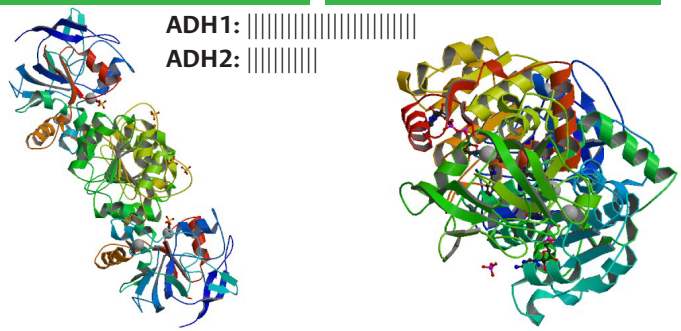
E.C: 1.1.1.1

alcohol[c] + NAD(+)[c] ⇔ aldehyde[c] + NADH[c]

1.1.1.1

ADH2 | **ADH1**

ADH1: ||||||||||||||||||||||||||
ADH2: ||||||||||



(ADH2 or ADH1)

sum (ExprADH2 + ExprADH1)

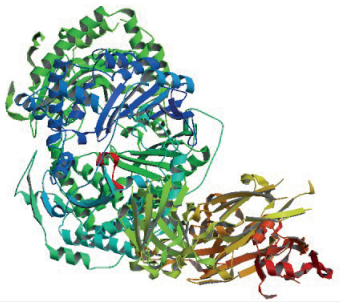
E.C: 3.4.21.5

polypeptides[e] ⇒ aminoacids[e]

3.4.21.5

IDE.A | **IDE.B** | **IDE.C**

IDE.A: ||||||||||||||||||||||||||
IDE.B: ||||||||||
IDE.C: ||||||||||||||||||



(IDE.A and IDE.B and IDE.C)

min (ExprIDE.A, ExprIDE.B, ExprIDE.C)

GPR

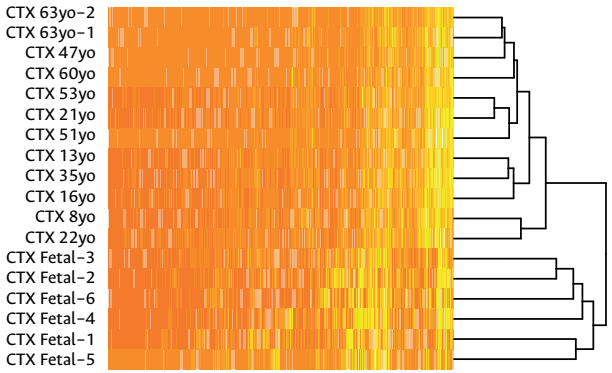
GENE EXPRESSION DATA →
METABOLIC MODEL WITH GPR →

exp2flux( )
CONVERT GENE EXPRESSION DATA TO FBA FLUXES →

CONSTRAINED METABOLIC MODEL →

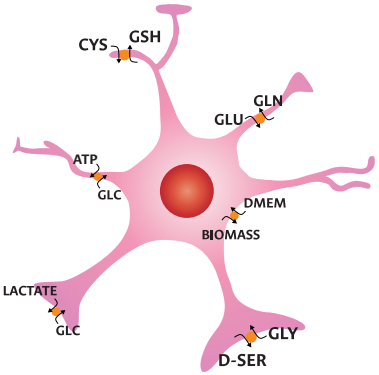
fluxDifferences( )
COMPUTE FOLDCHANGE OF FLUXES BETWEEN METABOLIC SCENARIOS

Human Healthy Mature Astrocyte Model



Expression Profile
GEO: GSE73721
Human Healthy Astrocytes
Zhang *et al.* (2016)

SBML
ASTROCYTE
Tissue Specific Model
GiBBSLab. (2016)

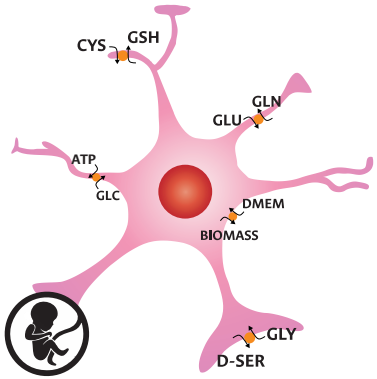


'exp2flux' Package

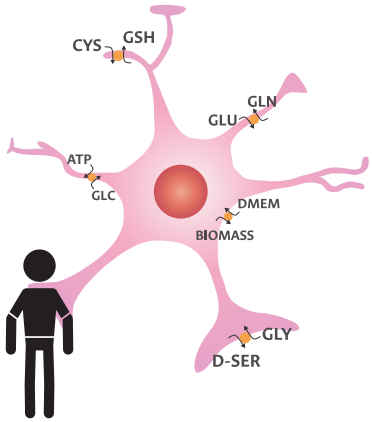
An R Package to convert expression data to FBA fluxes

Daniel Osorio, *Kelly Botero*, *Janneth Gonzalez* and *Andres Pinzón-Velasco*.

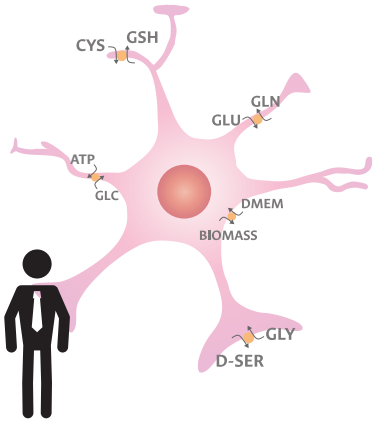
exp2flux()
CONVERT GENE EXPRESSION DATA TO FBA FLUXES



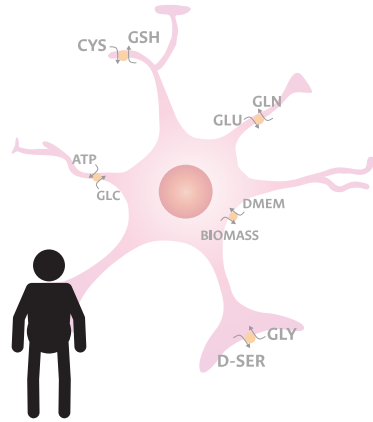
FETAL



YOUNG
8 - 16 yo.



ADULT
21 - 35 yo.



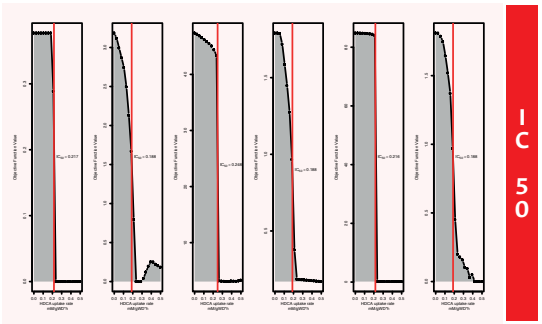
MATURE
47 - 63 yo.

OBJECTIVE 2:

Evaluate the effects caused by the increase of free fatty acids and tibolone presence in astrocytes metabolism.

Metabolic Scenarios

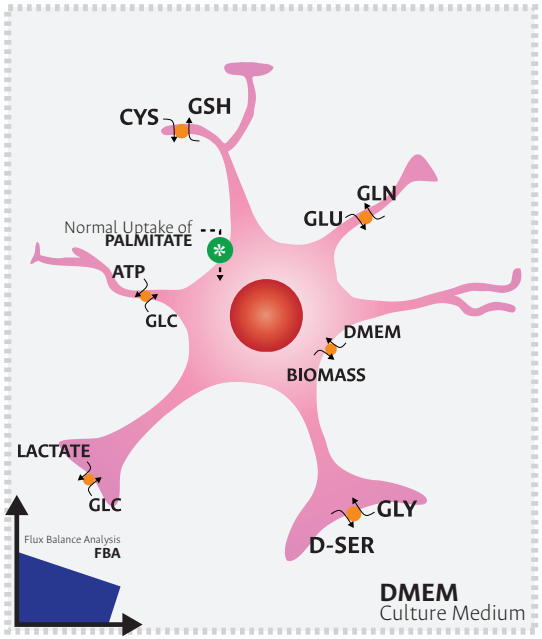
Normal Uptake of **PALMITATE**



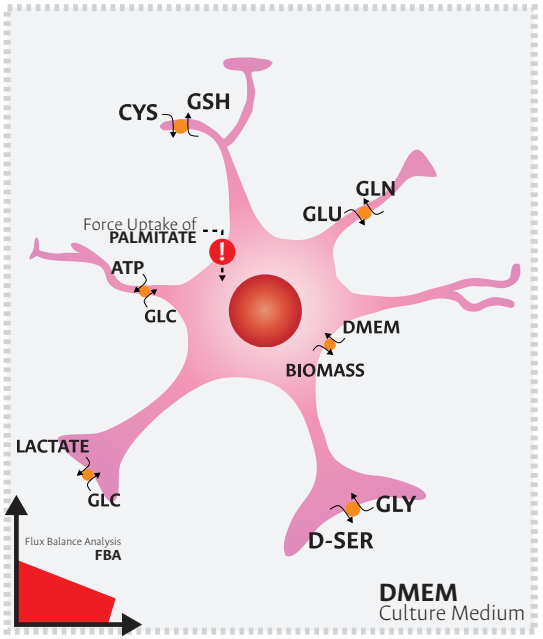
Force Uptake of **PALMITATE**

TIBOLONE

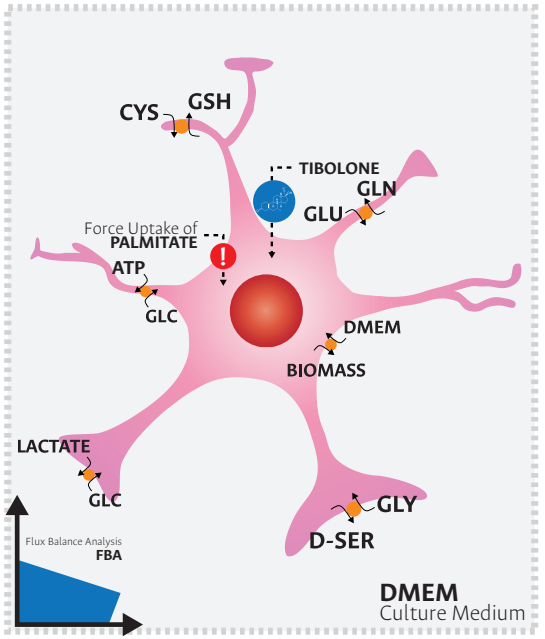
HEALTHY



INFLAMMATED



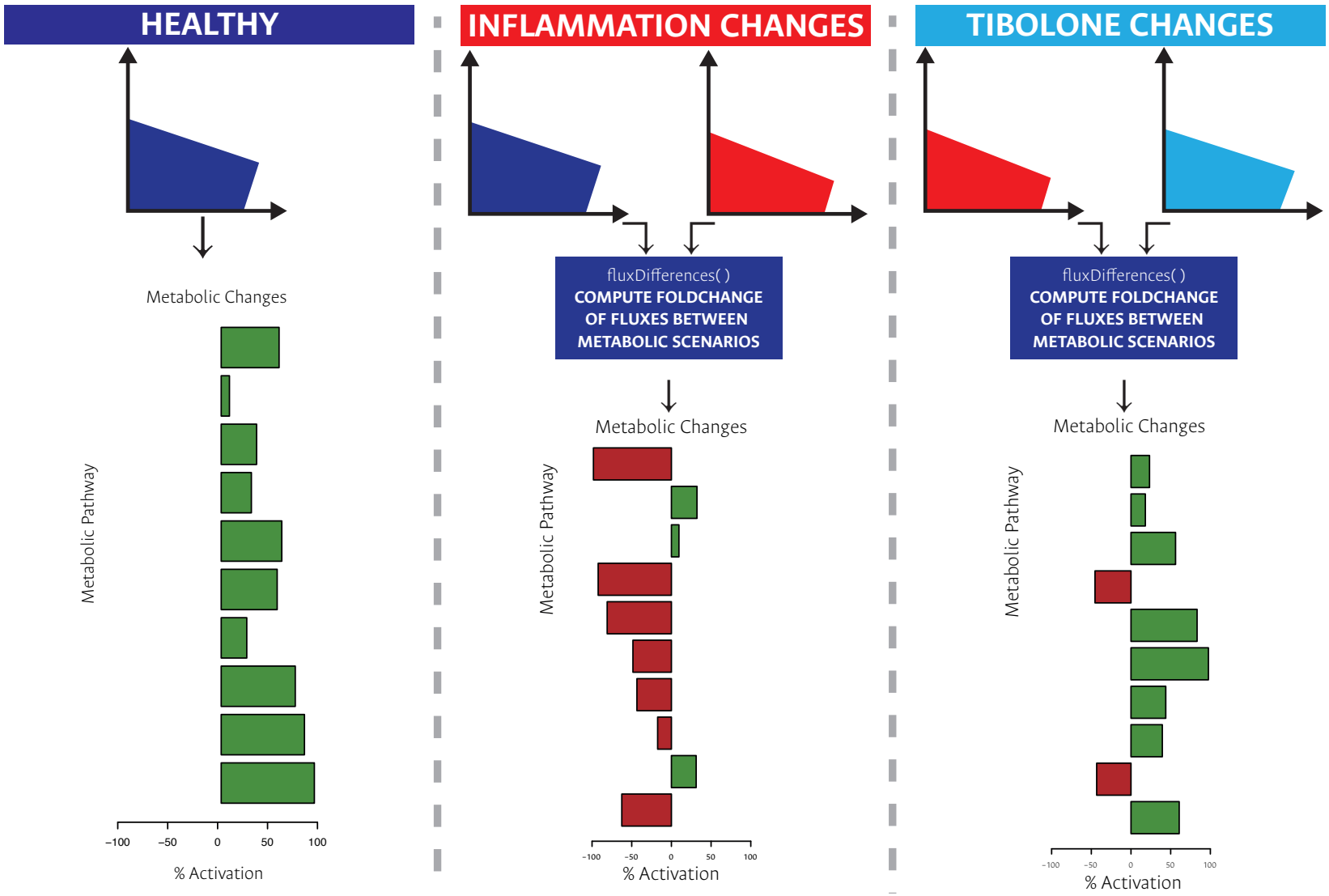
MEDICATED



OBJECTIVE 3:

Determine metabolic pathways and relevant functional products in response to steroid tibolone through systems biology approximations.

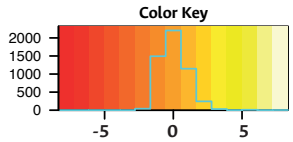
Metabolic Pathways Activation Pattern Changes



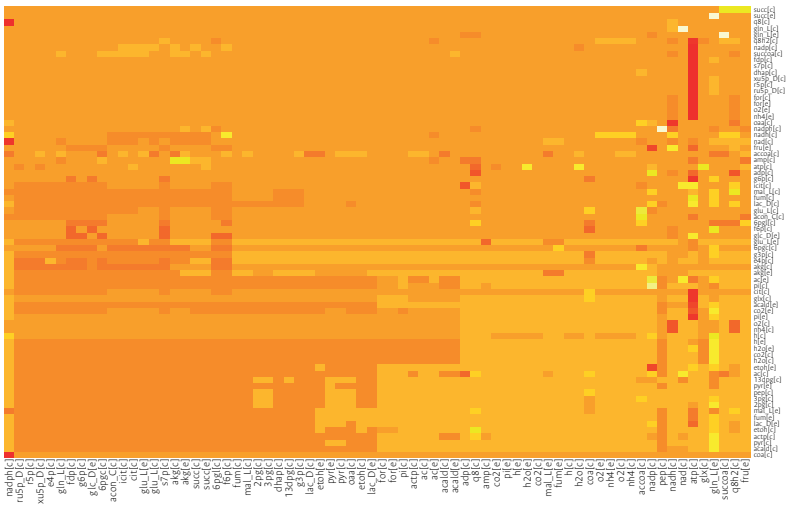
Changes in Metabolites Production

Now running at:

BIOS
CENTRO DE BIOINFORMÁTICA Y BIOLOGÍA COMPUTACIONAL
Conocimiento e innovación para el desarrollo



$$\textbf{foldChange} = \frac{\text{Scenario2 - Scenario1}}{|\text{Scenario1}|}$$

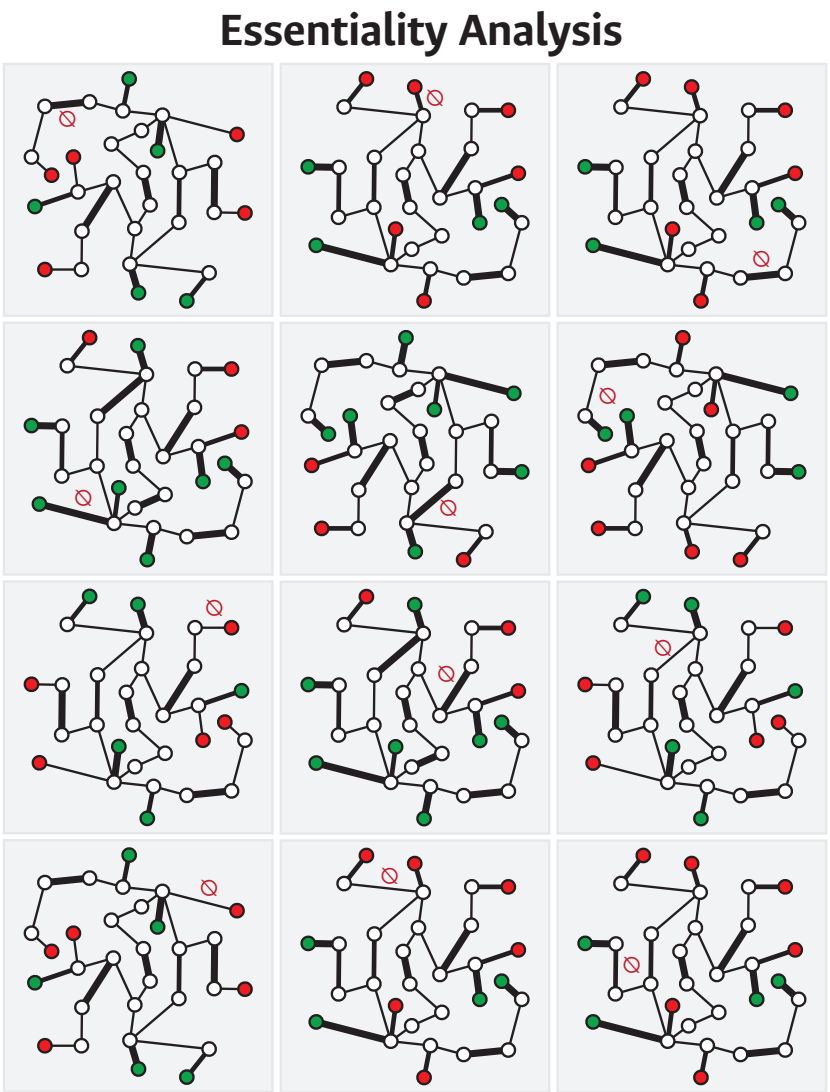


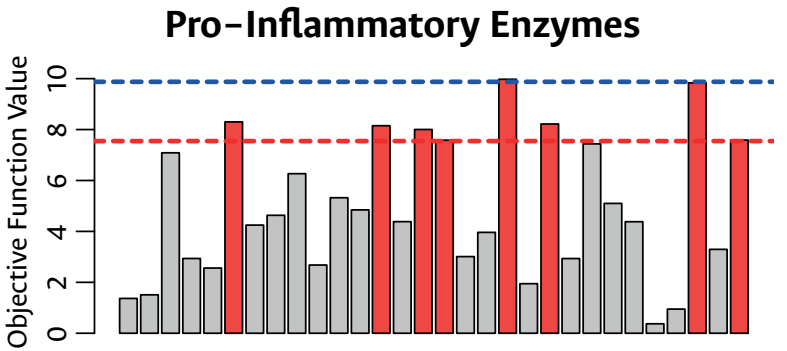
Inflammation Related
Metabolic Changes

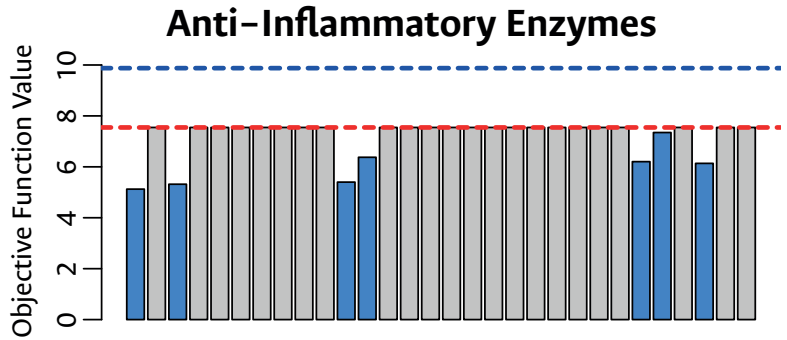
Tibolone Related
Metabolic Changes

OBJECTIVE 4:

Evaluate the importance of proteins and metabolic pathways previously identified on the dynamics of the metabolic model.


Essentiality Analysis


Pro−Inflammatory Enzymes
Objective Function Value
0
2
4
6
8
10


Anti−Inflammatory Enzymes
Objective Function Value
0
2
4
6
8
10

Software Packages

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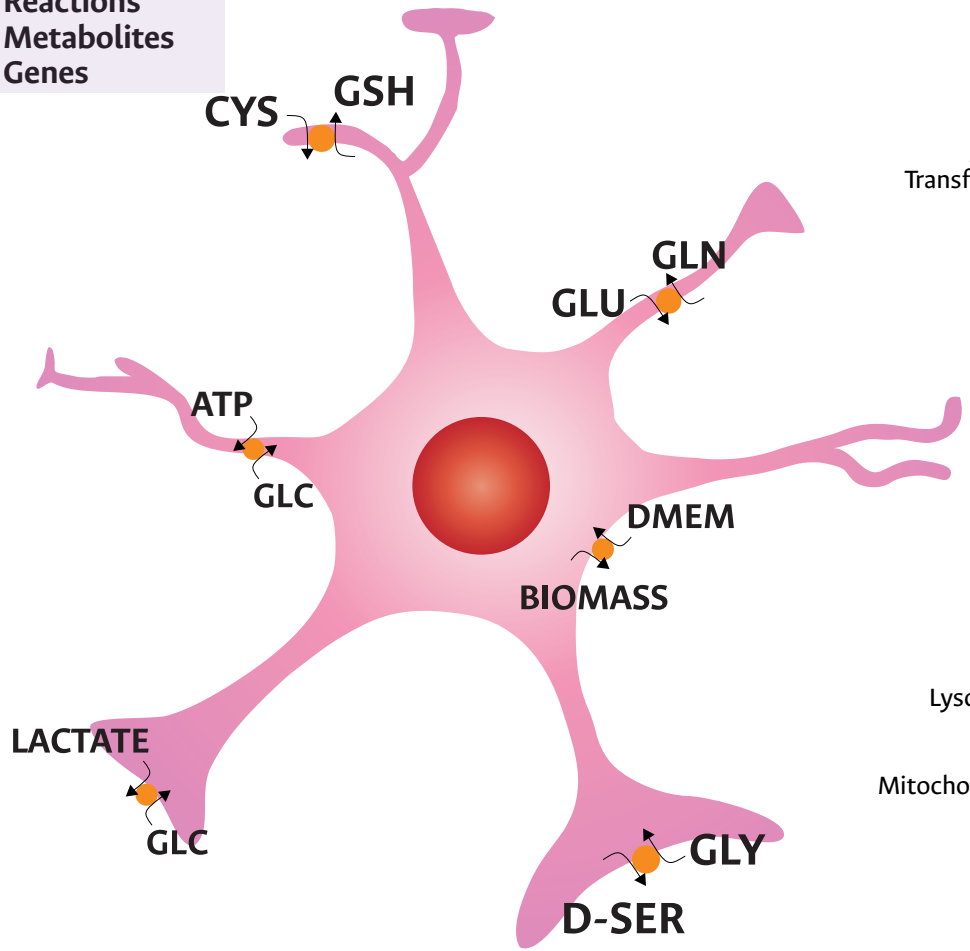
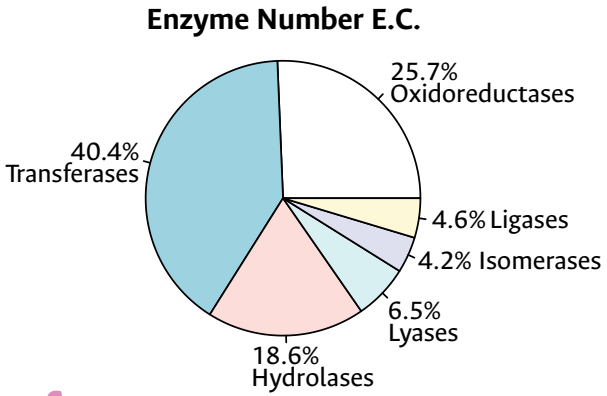
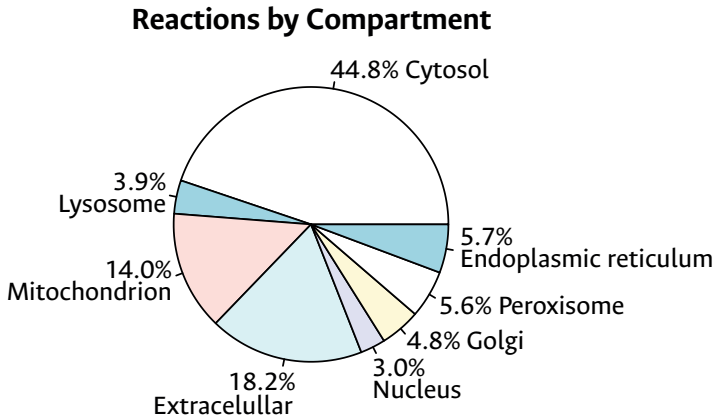
Astrocyte Model

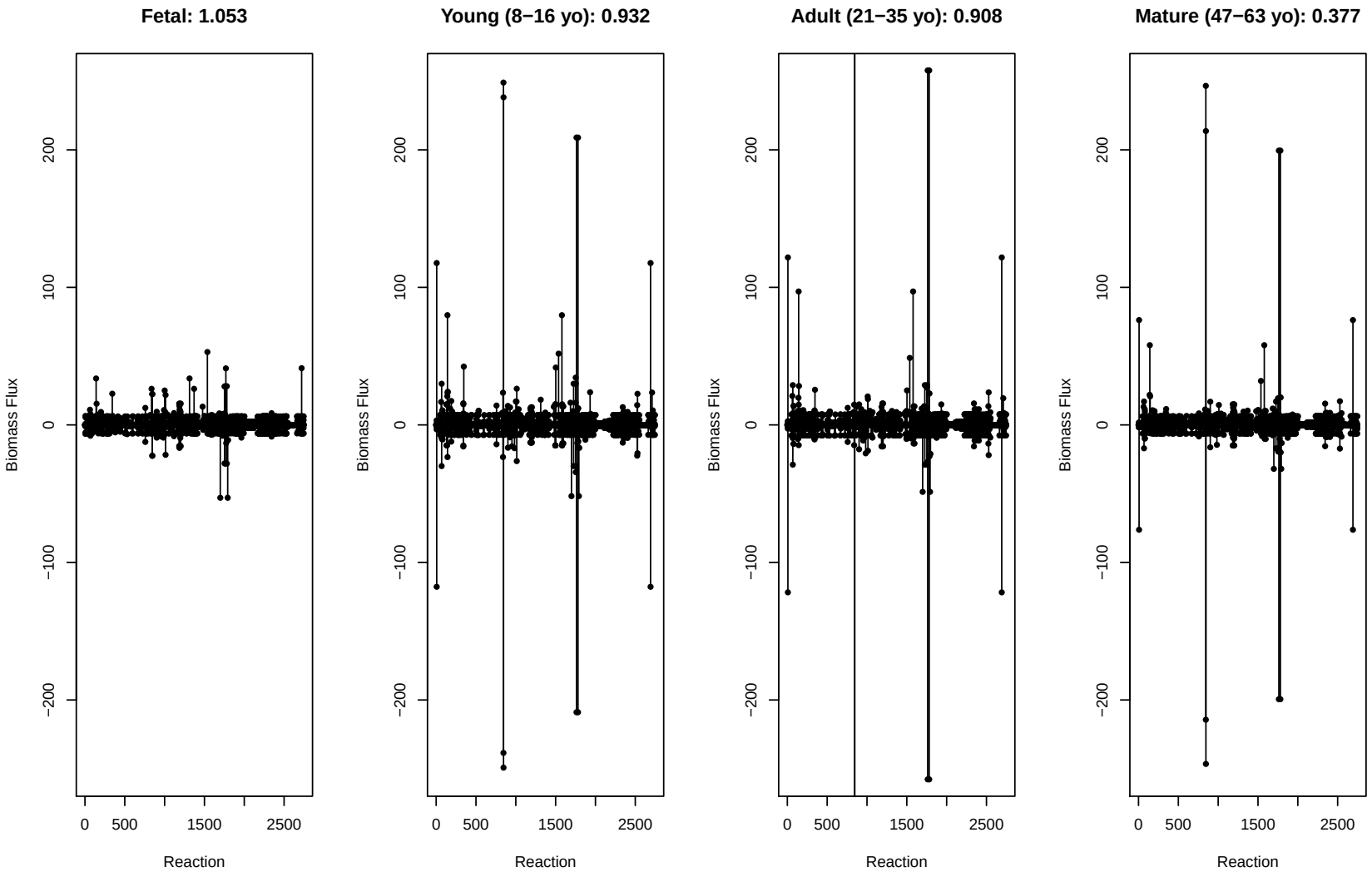
8 **Compartments**
2747 **Reactions**
1956 **Metabolites**
1262 **Genes**



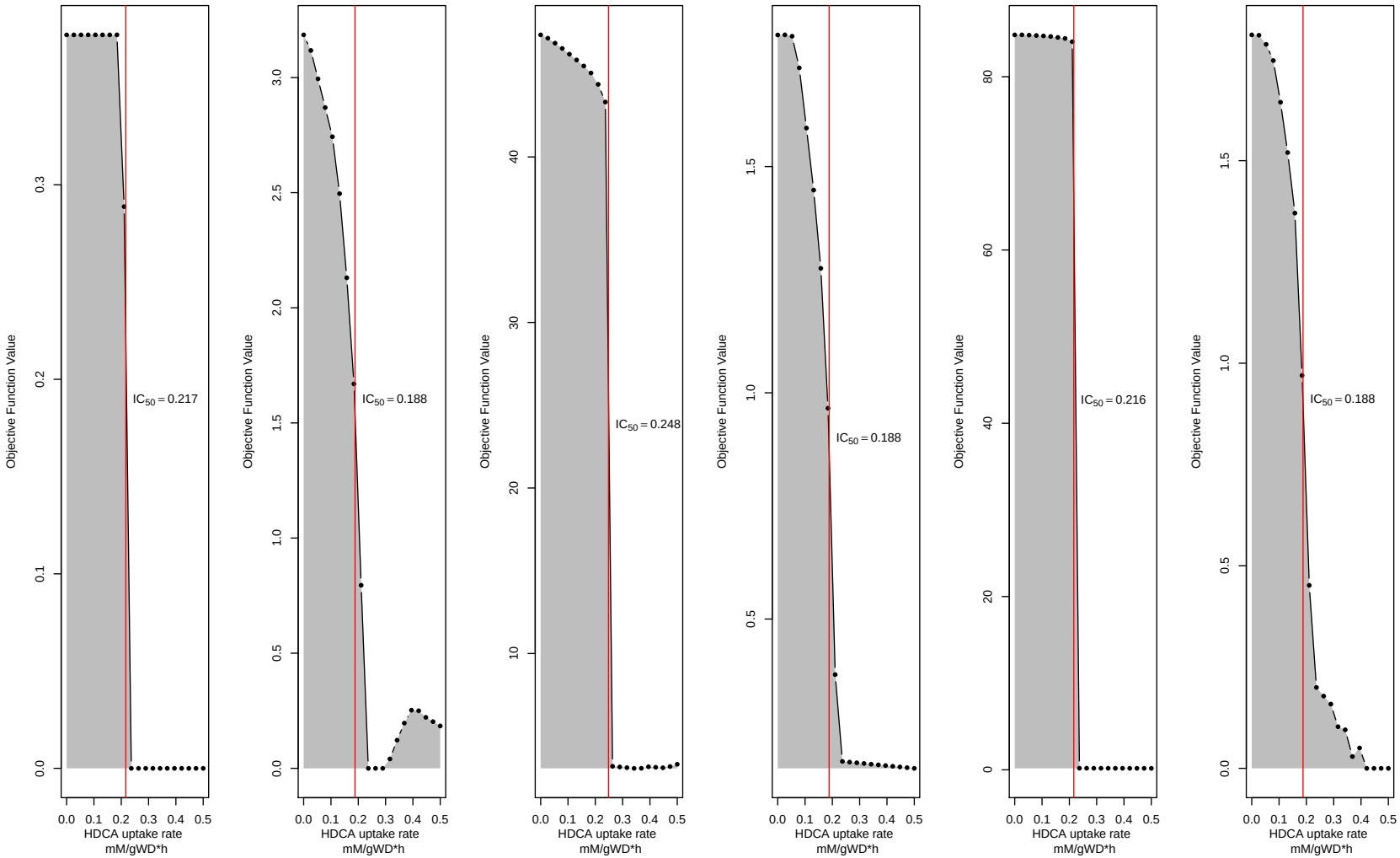




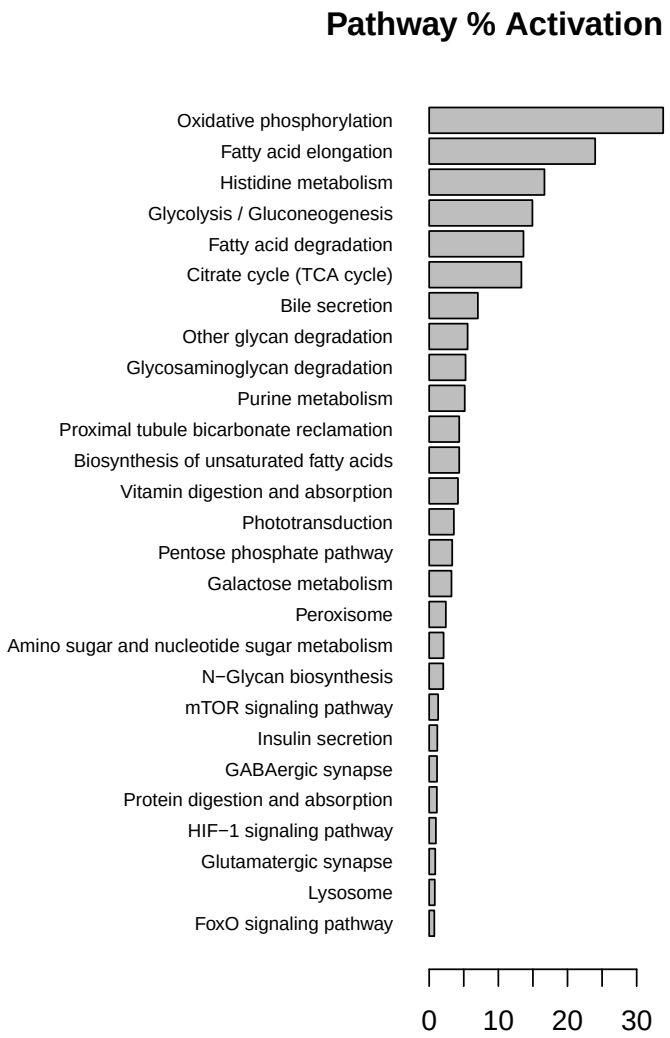
Age Related Metabolic Changes in Astrocytes

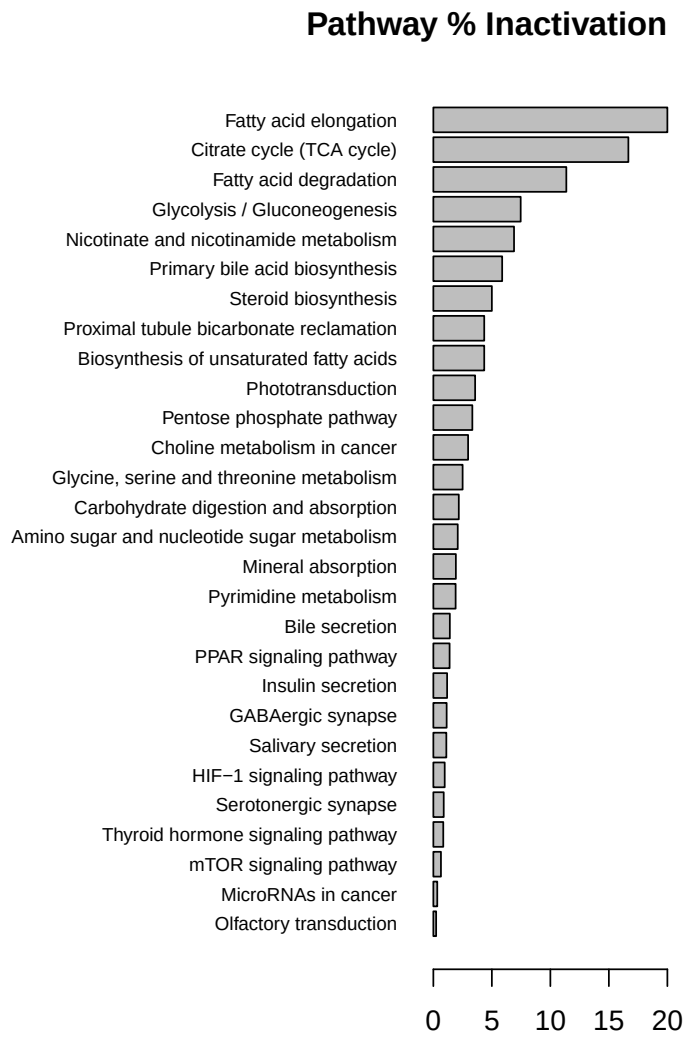


$IC_{50} = 0.208 \pm 0.024$ $mMgDW^{-1}h^{-1}$

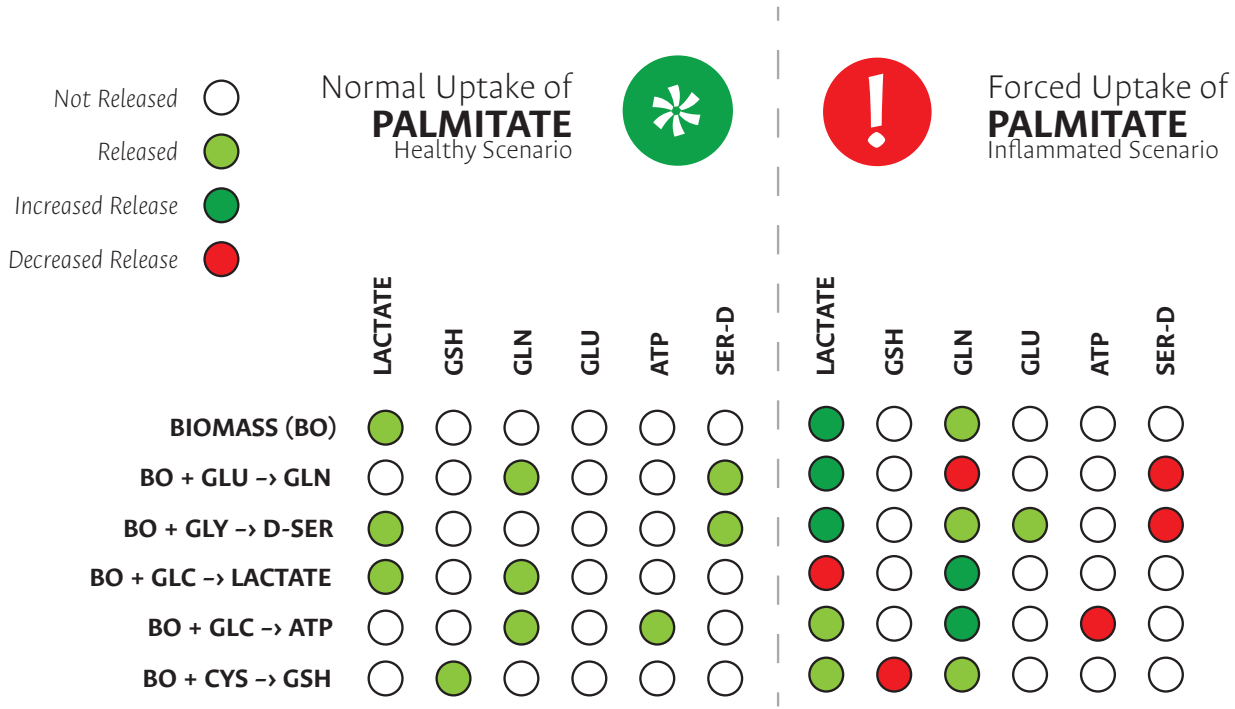


Inflammation Related Metabolic Changes in Astrocytes

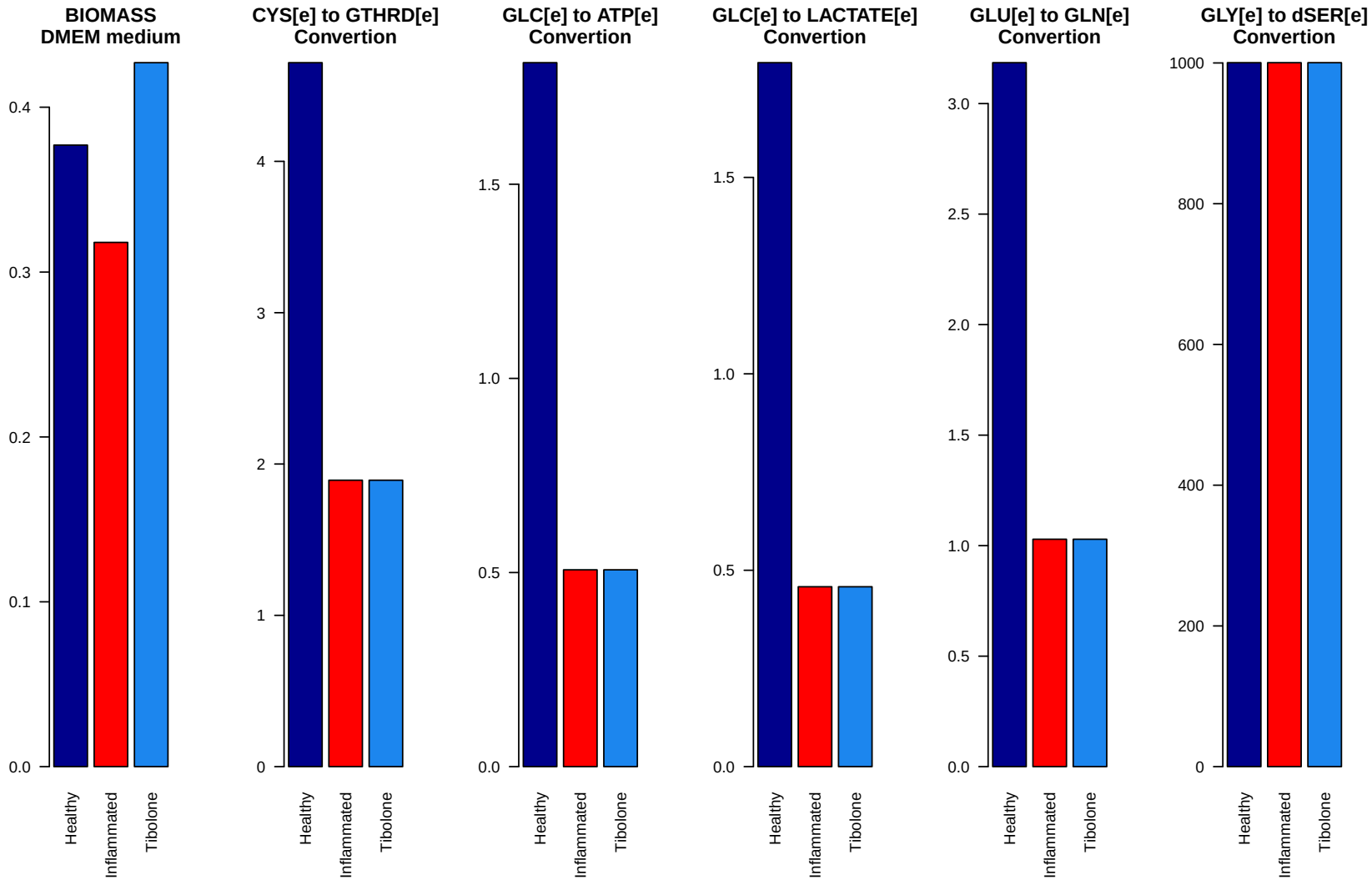




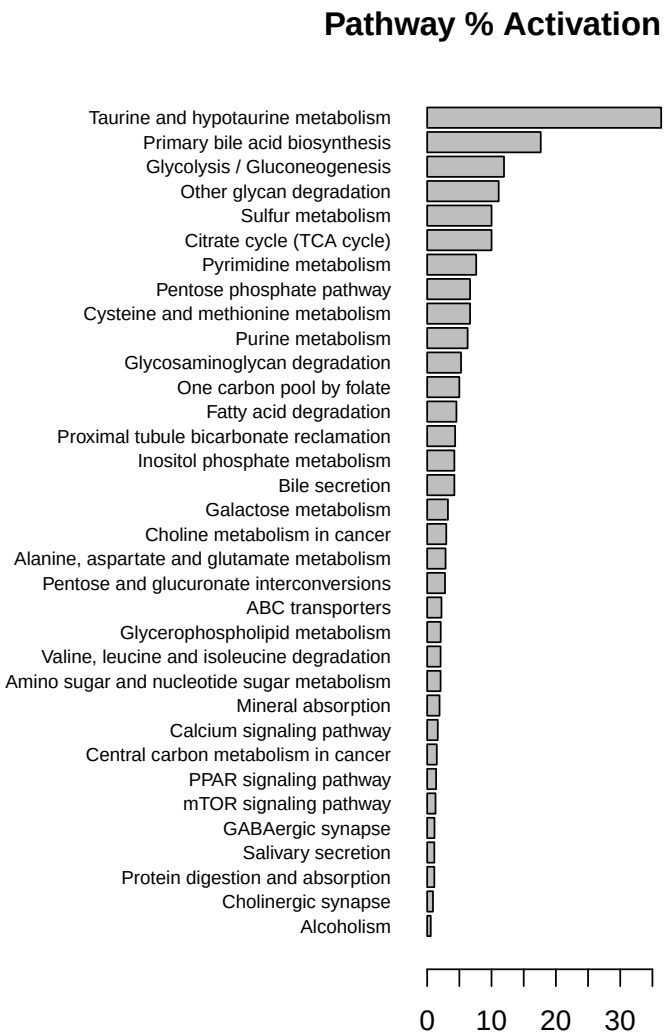
Gliotransmitters Release Rate

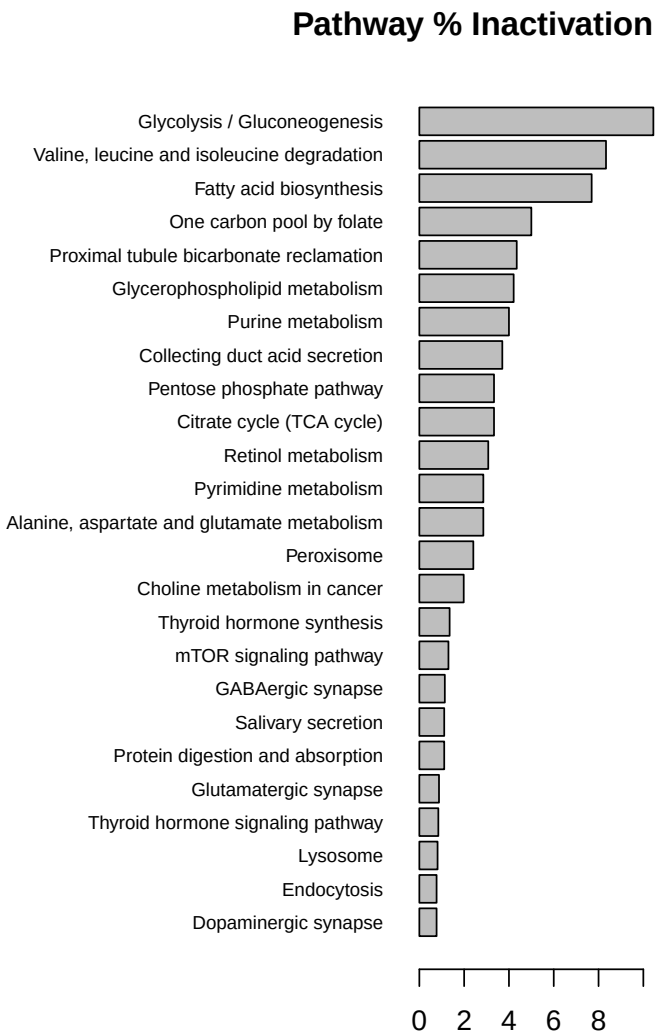


Tibolone Effects in Inflammated Astrocytes

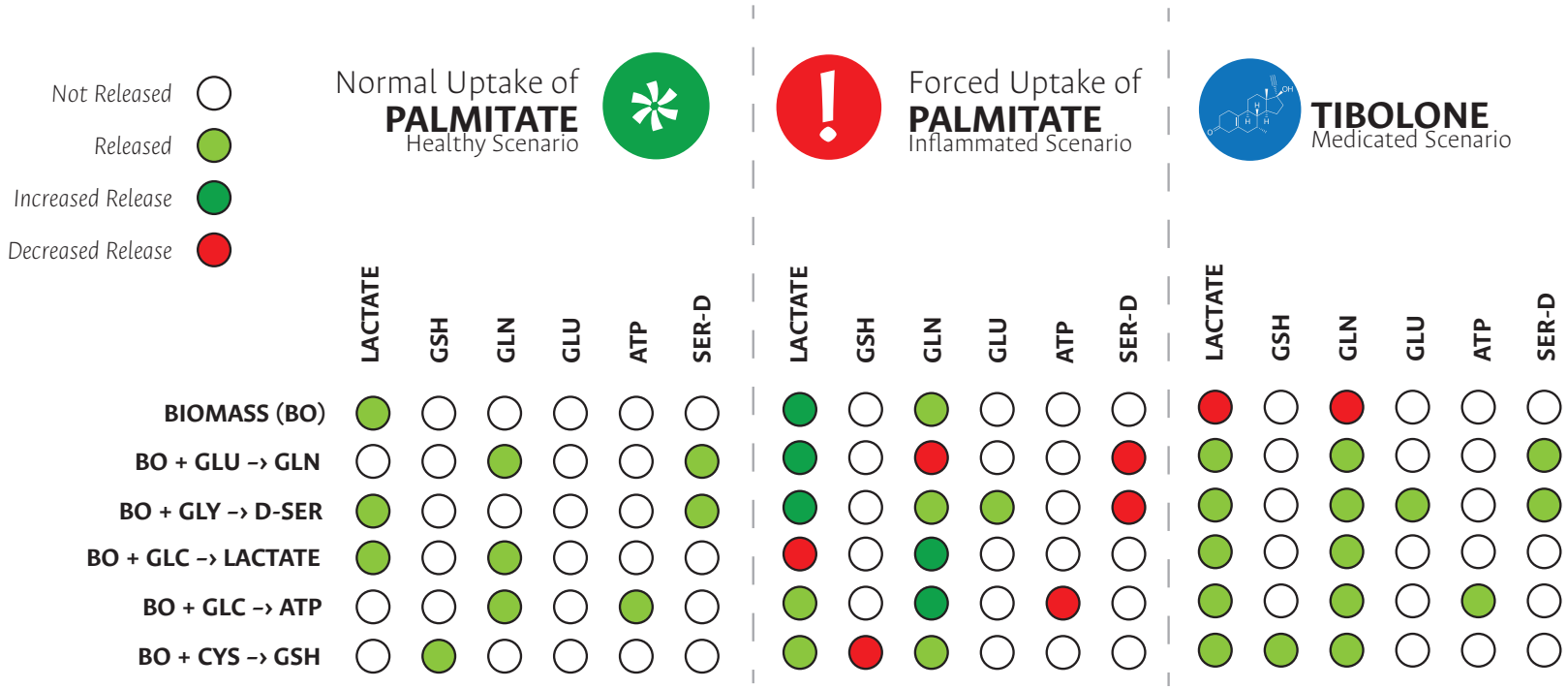


Tibolone Metabolic Changes in Inflammated Astrocytes





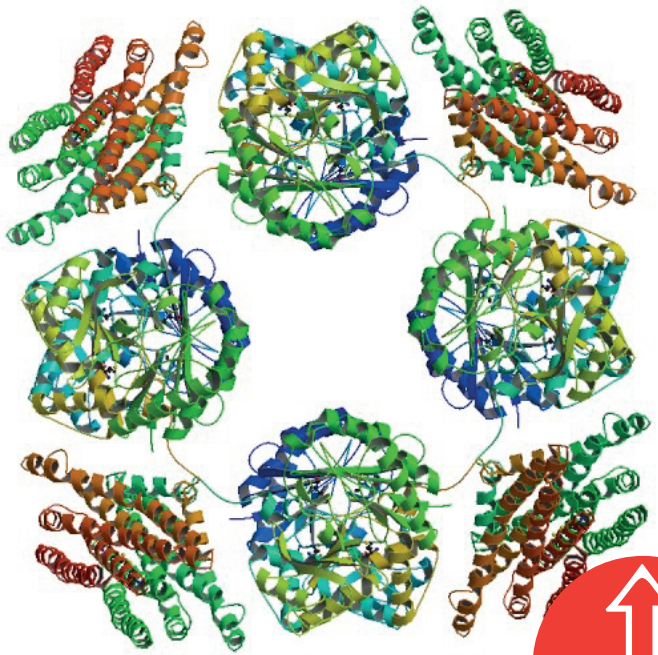
Gliotransmitters Release Rate



ProInflammatory Enzymes

FTCD

FormimidoylTransferase CycloDeaminase



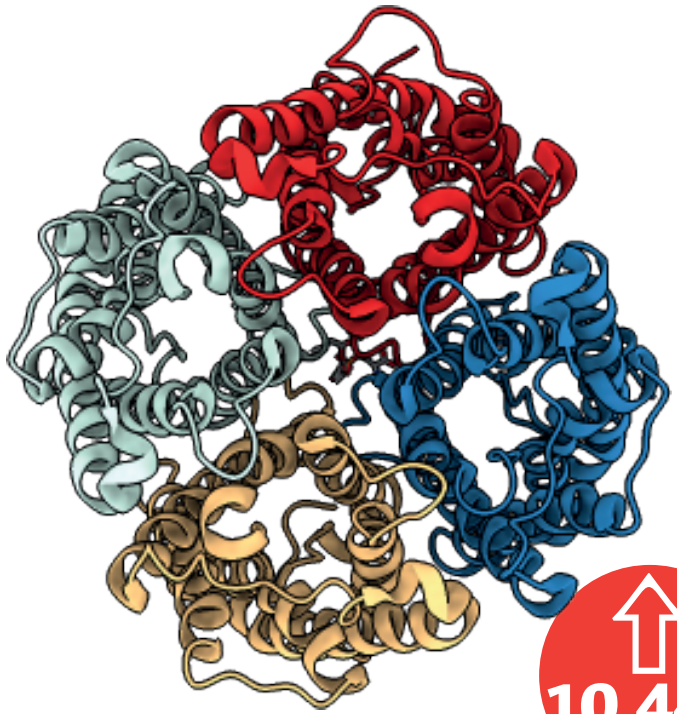
EC: 4.3.1.4 **EC:** 2.1.2.5

2 h[c] + 5forthf[c] ⇔ nh4[c] + methf[c]

2.2X
11.44%

H2Otm

H2O Transport Mitochondrial



h2o[c] ⇔ h2o[m]

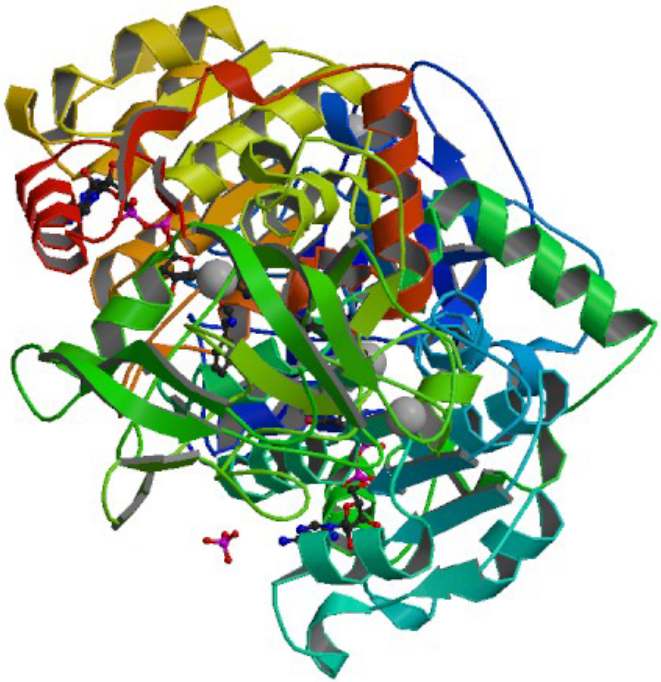
10.44X
5.14%

74 Anti inflammatory Enzymes

Tibolone Related Enzymes

r0739

Alcohol Dehydrogenase 1 - 7

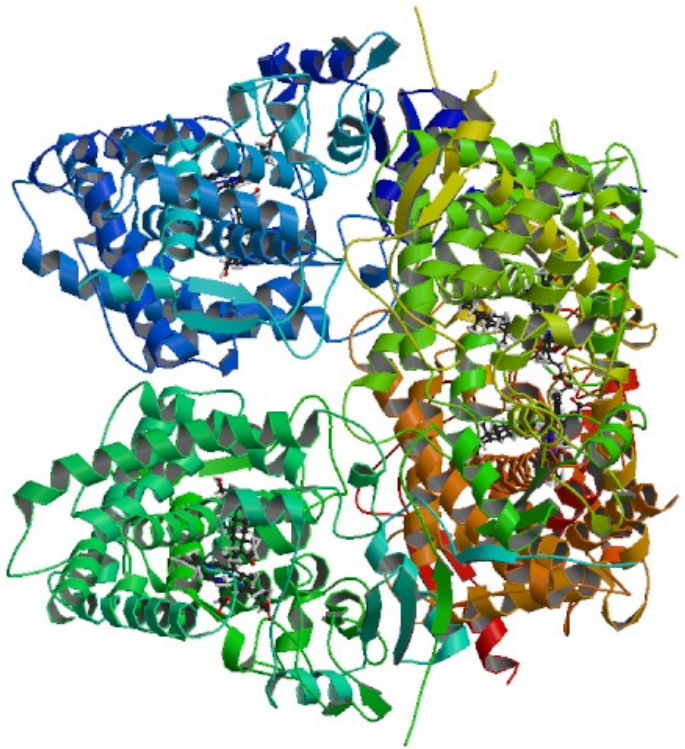


EC: 1.1.1.1

nad[c] + xol7ah3[c] ⇔ h[c] + nadh[c] + xol7ah2al[c]

REM1804m | REM1807m

Cytochrome P450 Family 27 Subfamily A Member 1



EC:1.14.15.15

nad[c] + xol7ah3[c] ⇔ h[c] + nadh[c] + xol7ah2al[c]

Advances of this work were presented as:

Metabolic inflammation effects over the gliotransmitters release in mature astrocytes: a network-based approach.

Daniel Osorio MSc., Janneth Gonzalez PhD., Andrés Pinzón-Velasco PhD.
Bioinformatics and Computational Systems Biology Lab, Universidad Nacional de Colombia.

at:

CDMX, México
Short Talk

Barcelona, España
Poster

Bogotá, Colombia
Short Talk

This study is under development at the:

Bioinformatics and Computational Systems Biology Lab

Institute for Genetics - Universidad Nacional de Colombia

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