

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

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Facultad de Ciencias, Pontificia Universidad Javeriana - Bogotá

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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 → ▲ IKK β + ▲ NF $\kappa\beta$

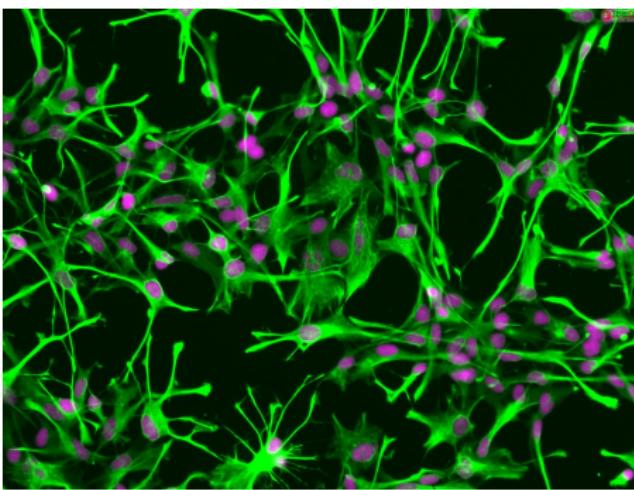
Metabolic Inflammation or Metainflammation

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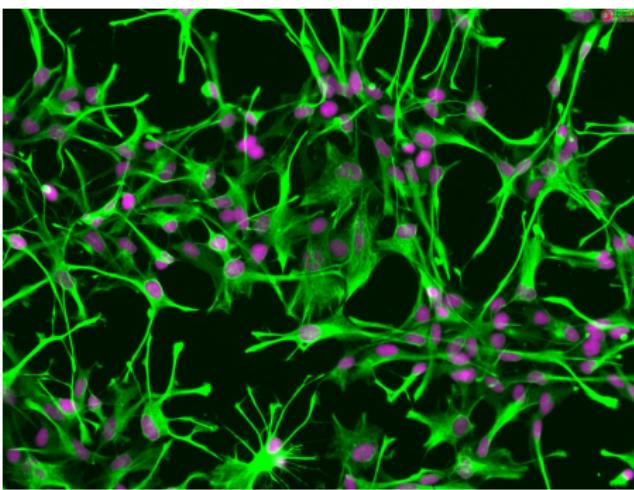
▲ Endoplasmic reticulum stress → ▲ UPR

▲ Reactive C Protein Ligands + ▲ TNF α + ▲ IL6 + ▲ ROS

Astrocytes Metabolic Functions

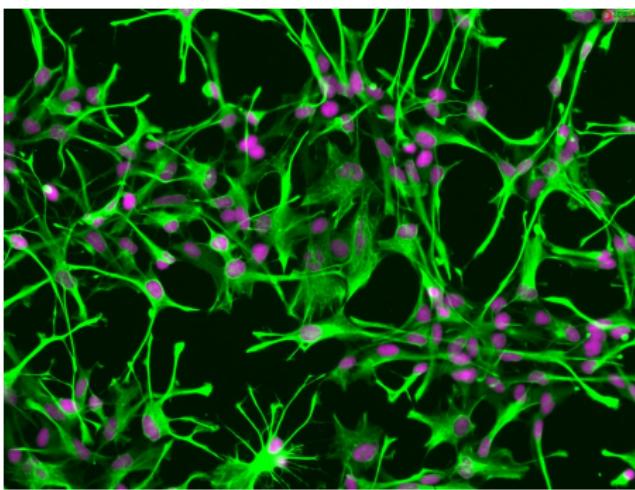


Astrocytes Metabolic Functions



K^+ Membrane Potential

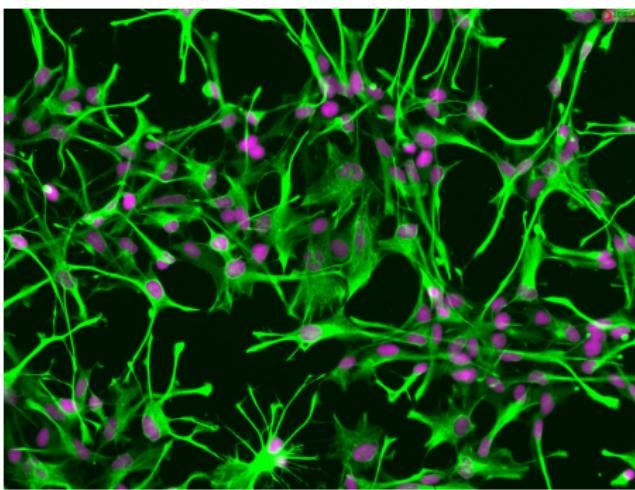
Astrocytes Metabolic Functions



K^+ Membrane Potential

Ca^{2+} signaling

Astrocytes Metabolic Functions

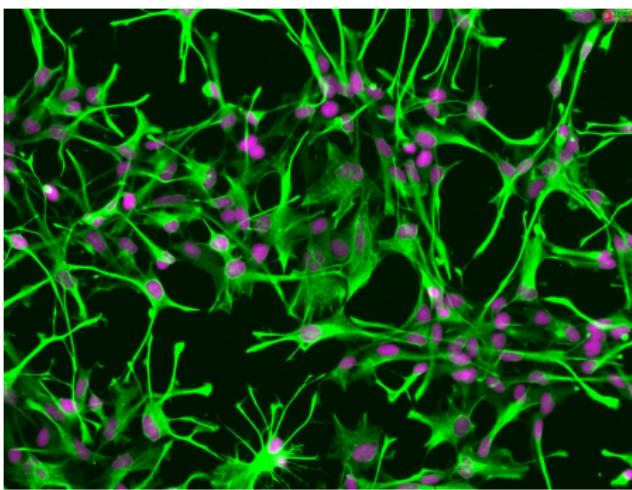


K^+ Membrane Potential

Ca^{+2} signaling

Lactate release

Astrocytes Metabolic Functions



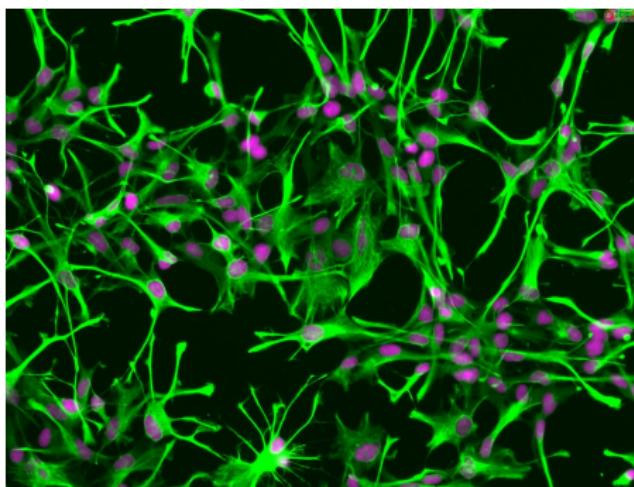
K^+ Membrane Potential

Ca^{+2} signaling

Lactate release

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

Astrocytes Metabolic Functions



K^+ Membrane Potential

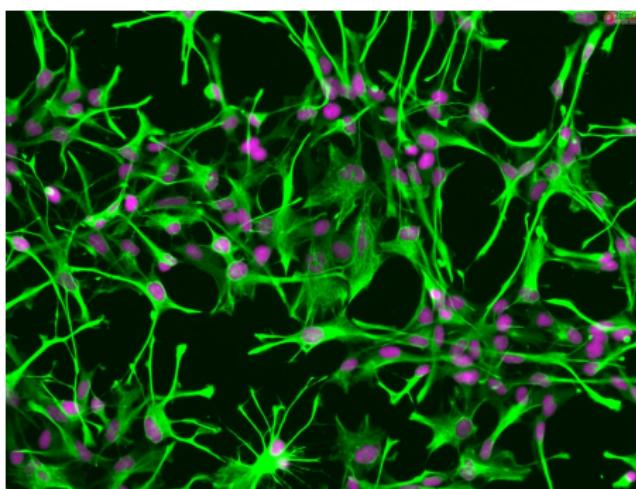
Ca^{+2} signaling

Lactate release

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

pH maintenance

Astrocytes Metabolic Functions



K^+ Membrane Potential

Ca^{+2} signaling

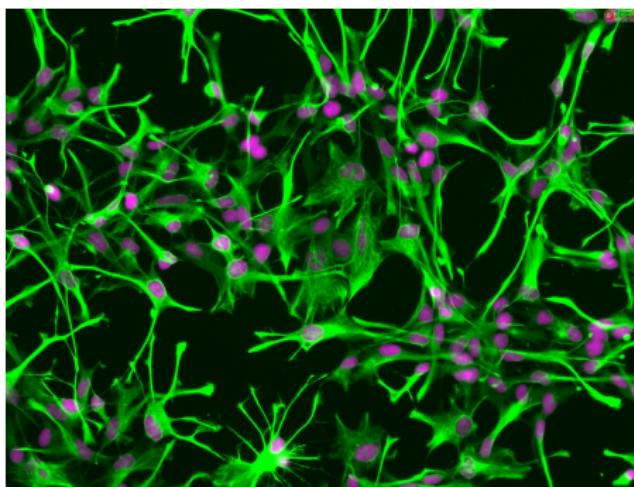
Lactate release

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

pH maintenance

ROS detox

Astrocytes Metabolic Functions



K^+ Membrane Potential

Ca^{+2} signaling

Lactate release

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

pH maintenance

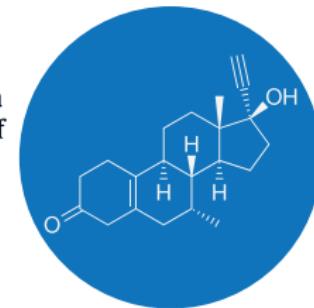
ROS detox

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:

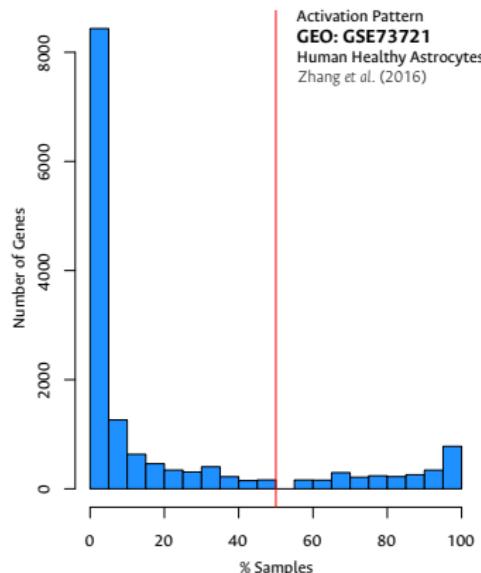
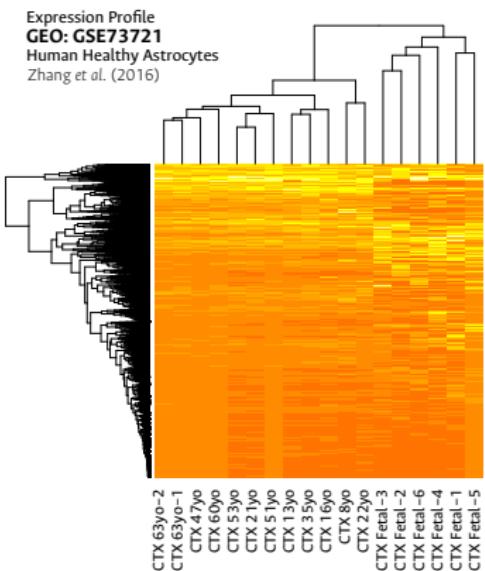
To identify proteins and metabolic pathways involved in the neuroprotective effects of tibolone in human astrocytes based in metabolic scenarios comparation we set:

- ▶ 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.

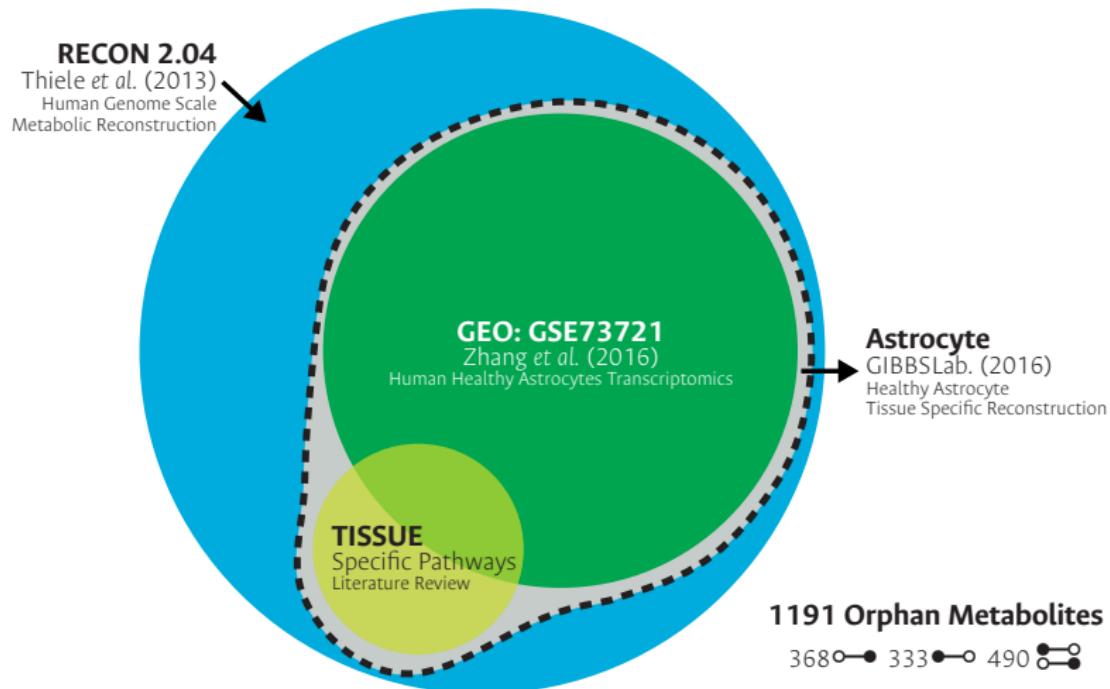
OBJECTIVE 1:

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

Human Astrocytes Gene Expression Data



Mapping Reactions



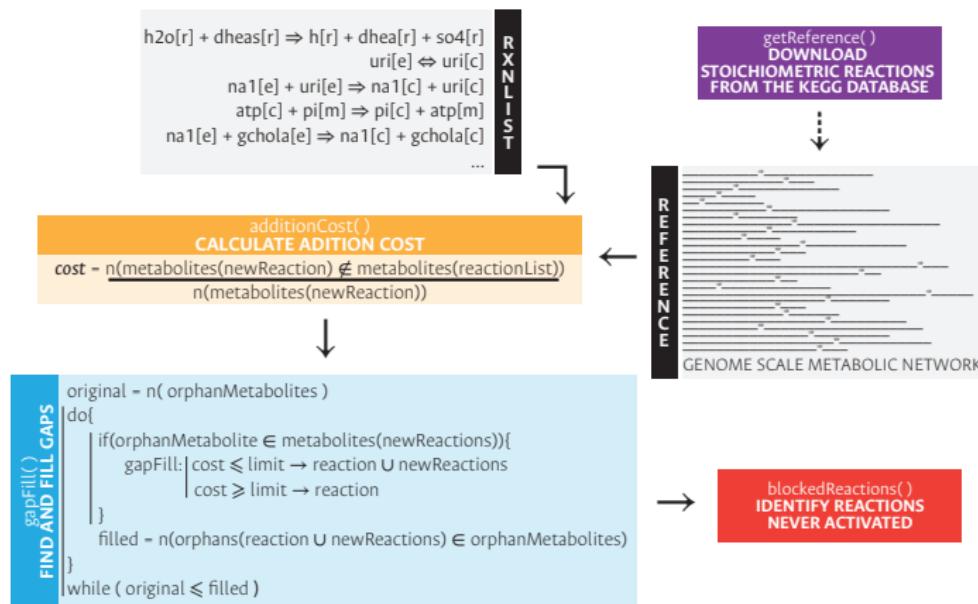
Software Development



'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



Software Development



'minval' Package

An R Package for MINimal VALidation of stoichiometric reactions

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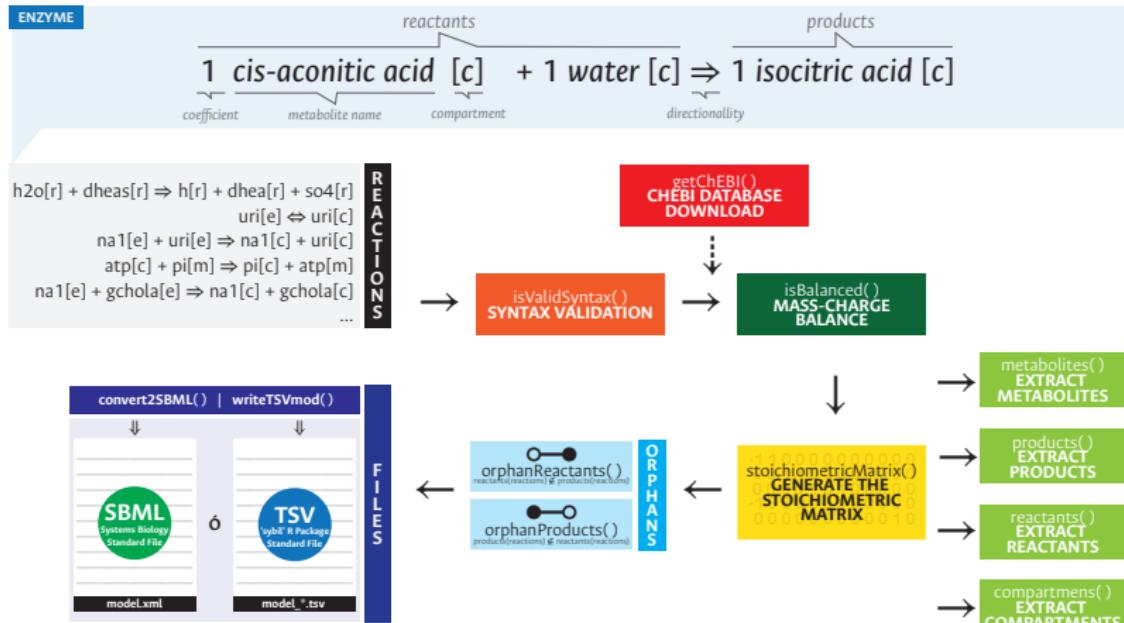
Language: R

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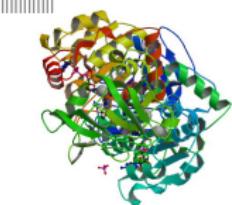
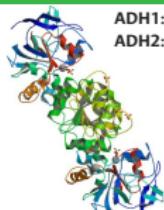
E.C: 1.1.1.1



1.1.1.1

ADH2

ADH1



(ADH2 or ADH1)

sum (ExprADH2 + ExprADH1)

E.C: 3.4.21.5



3.4.21.5

IDE.A

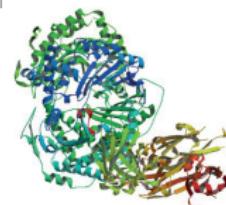
IDE.B

IDE.C

IDE.A:

IDE.B:

IDE.C:



GPR

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

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

GENE EXPRESSION
DATA



exp2flux()
CONVERT GENE
EXPRESSION DATA
TO FBA FLUXES



CONSTRAINED
METABOLIC MODEL

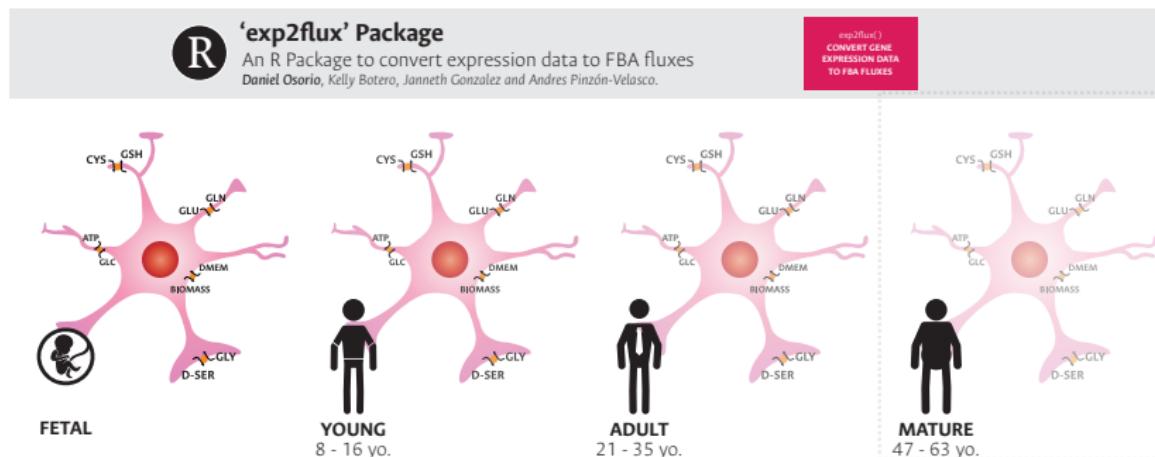
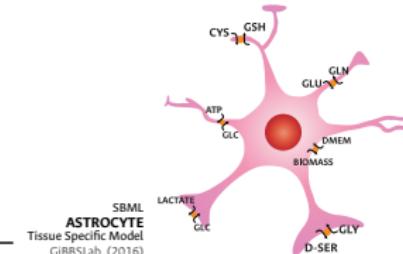
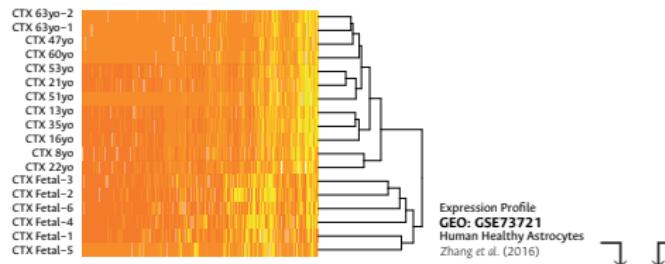


fluxDifferences()
COMPUTE FOLDCHANGE
OF FLUXES BETWEEN
METABOLIC SCENARIOS

METABOLIC MODEL
WITH GPR



Human Healthy Mature Astrocyte Model

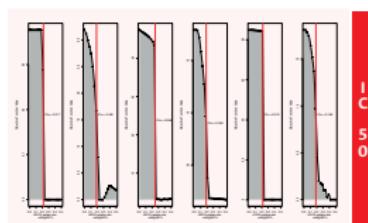


OBJECTIVE 2:

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

Metabolic Scenarios

Normal Uptake of PALMITATE



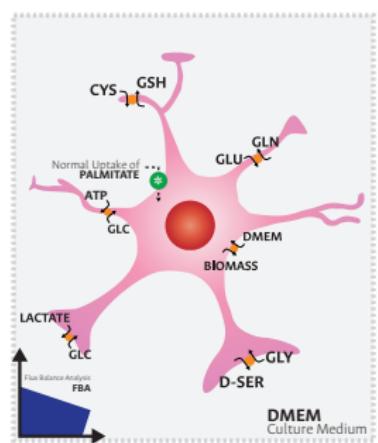
Force Uptake of PALMITATE



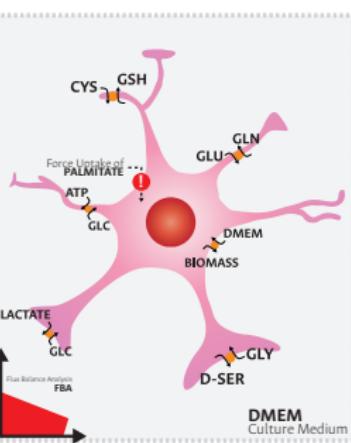
TIBOLONE



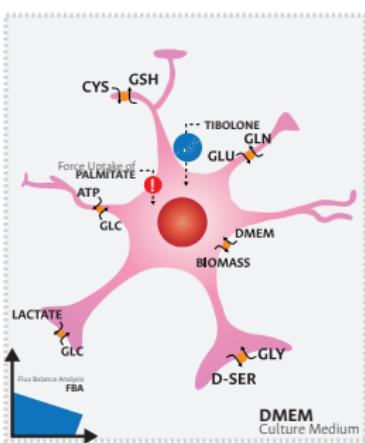
HEALTHY



INFLAMMATED



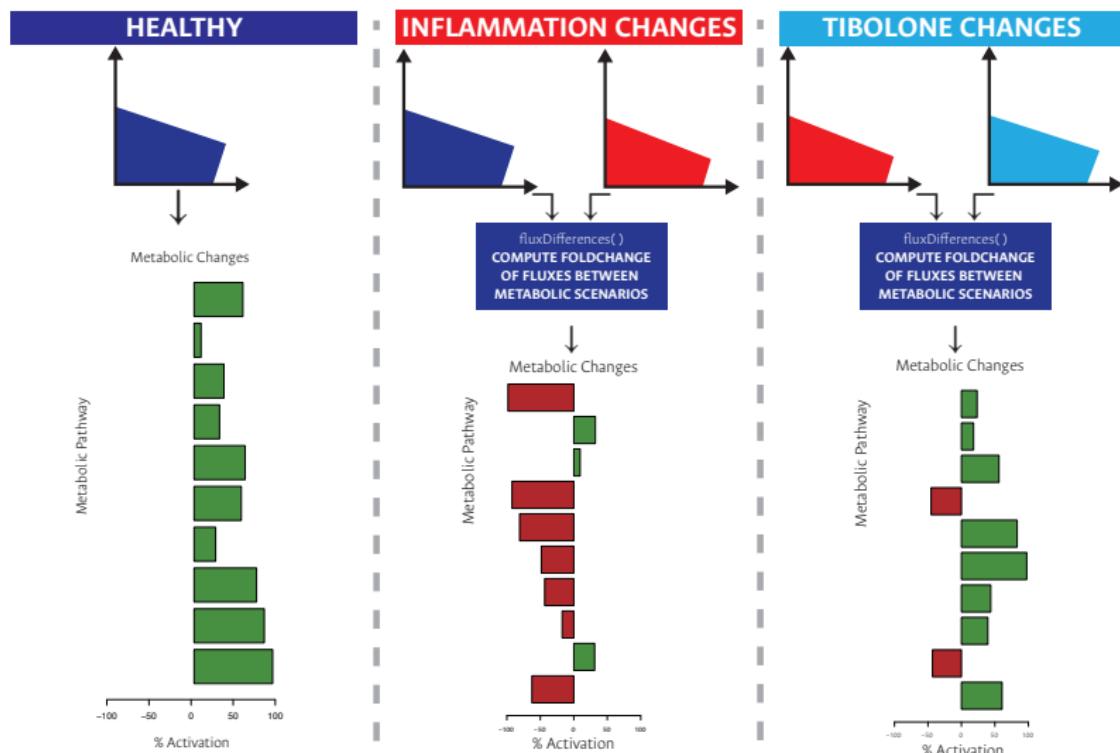
MEDICATED



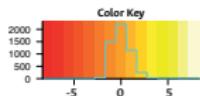
OBJECTIVE 3:

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

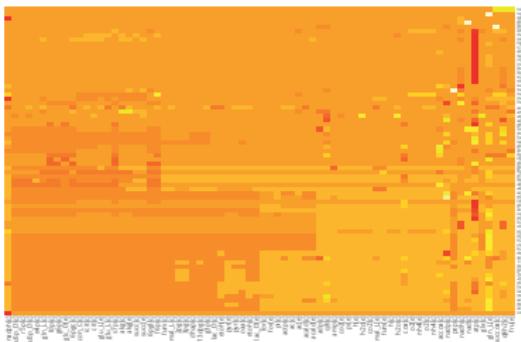
Metabolic Pathways Activation Pattern Changes



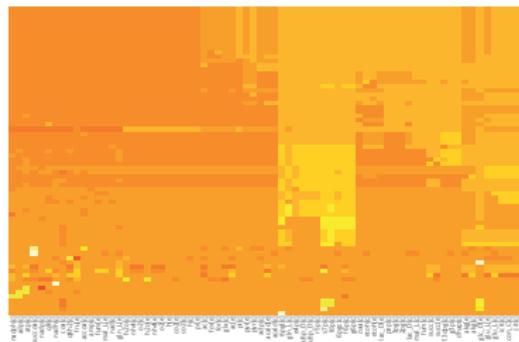
Changes in Metabolites Production



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



Inflammation Related
Metabolic Changes



Tibolone Related
Metabolic Changes

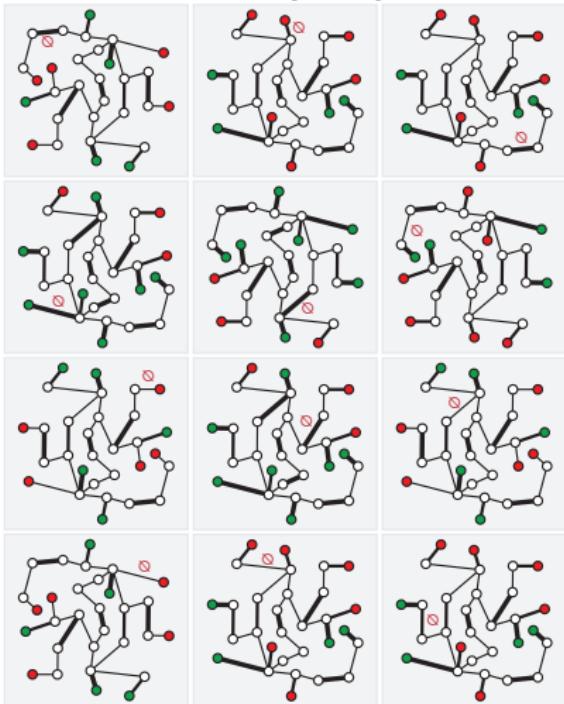
Now running at:



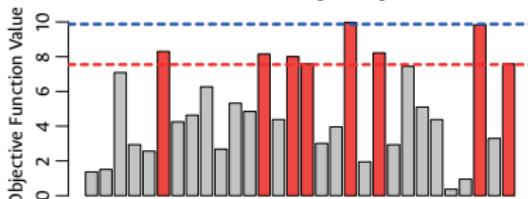
OBJECTIVE 4:

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

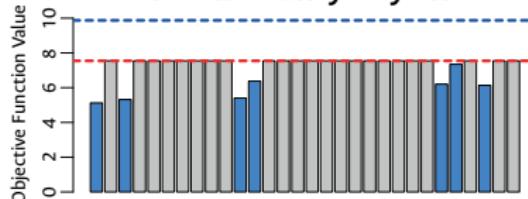
Essentiality Analysis



Pro-Inflammatory Enzymes



Anti-Inflammatory Enzymes



Software Packages



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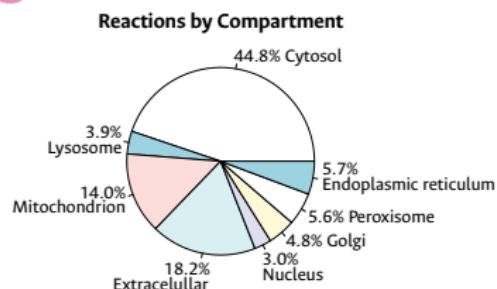
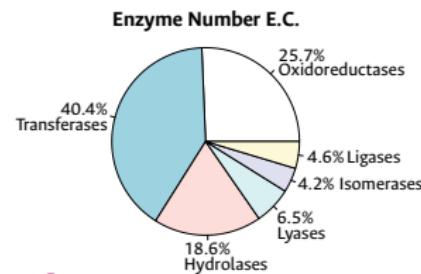
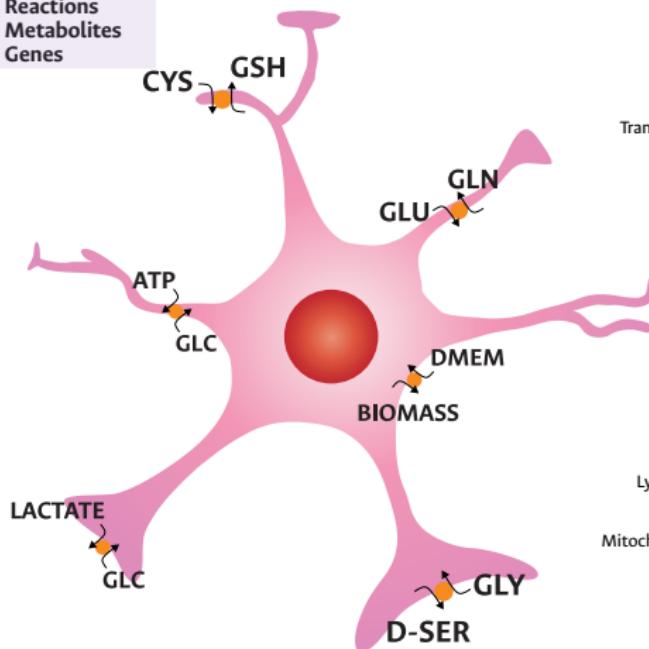
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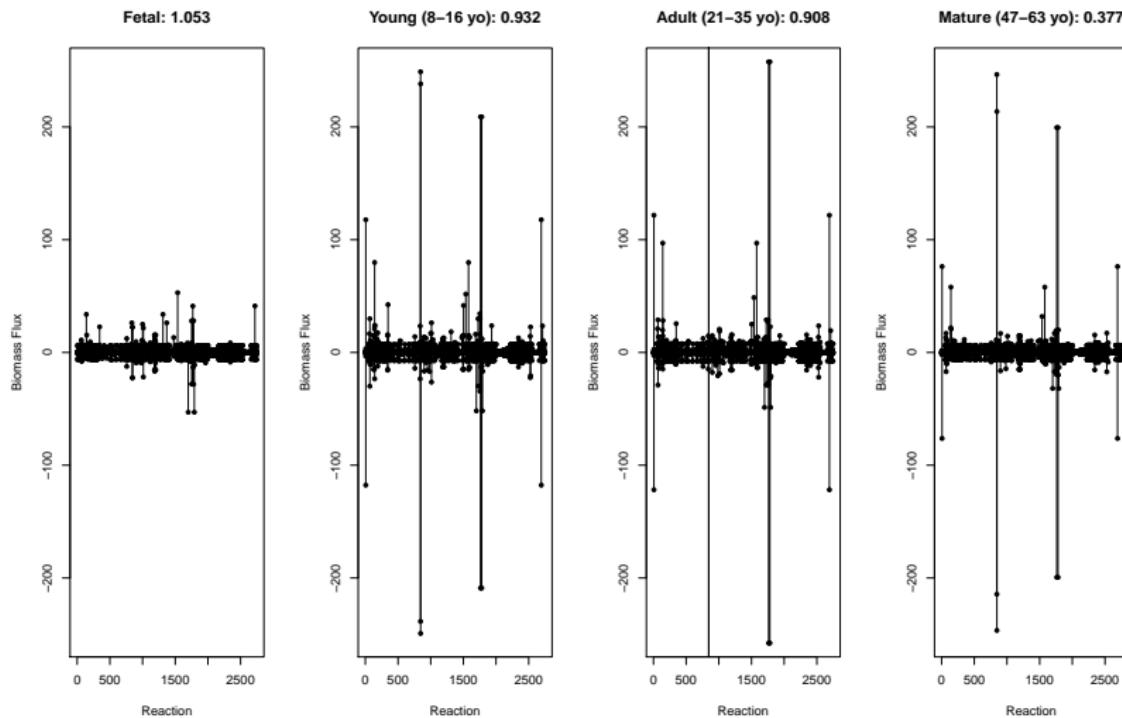
Language: R
Stable: CRAN
Development: gibbslab/exp2flux
License: GPL-2
Binaries: Windows - Linux - Mac

Astrocyte Model

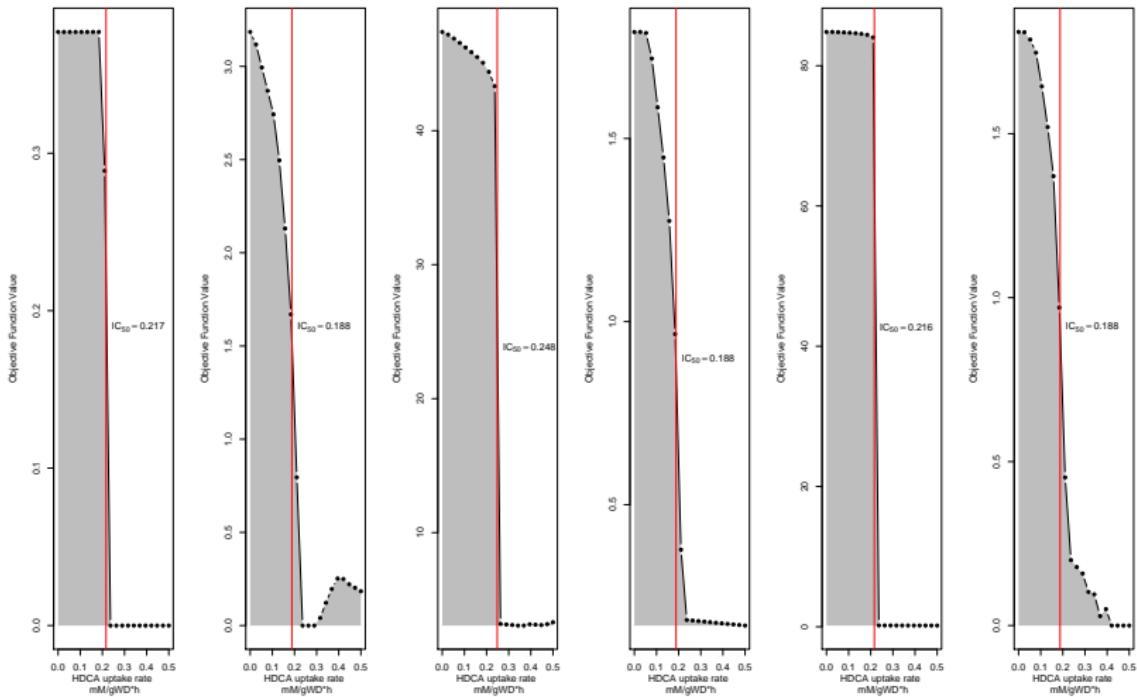
8 Compartments
2747 Reactions
1956 Metabolites
1262 Genes



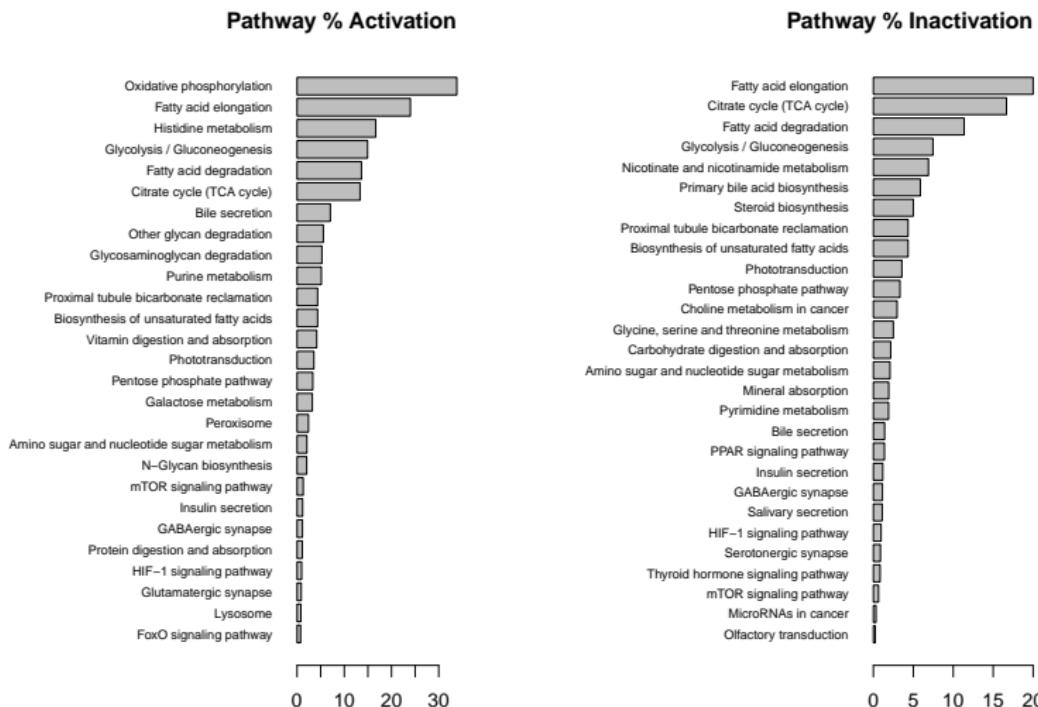
Age Related Metabolic Changes in Astrocytes



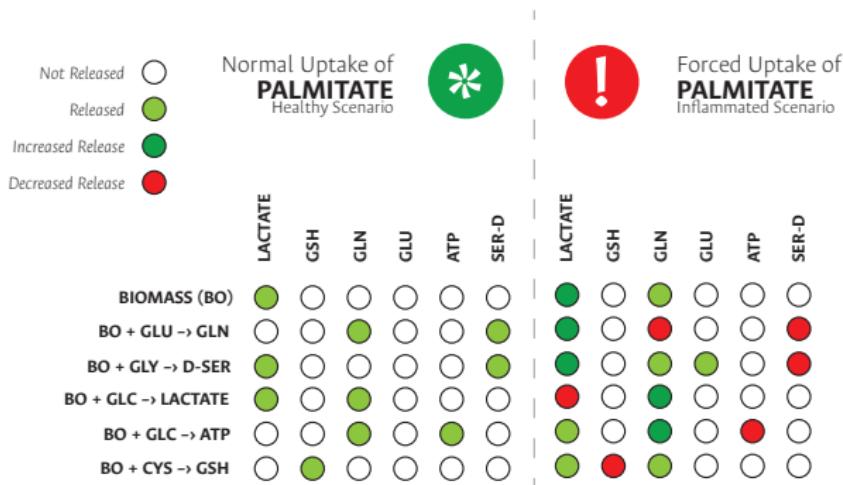
$$IC_{50} = 0.208 \pm 0.024 \text{ mMgDW}^{-1}\text{h}^{-1}$$



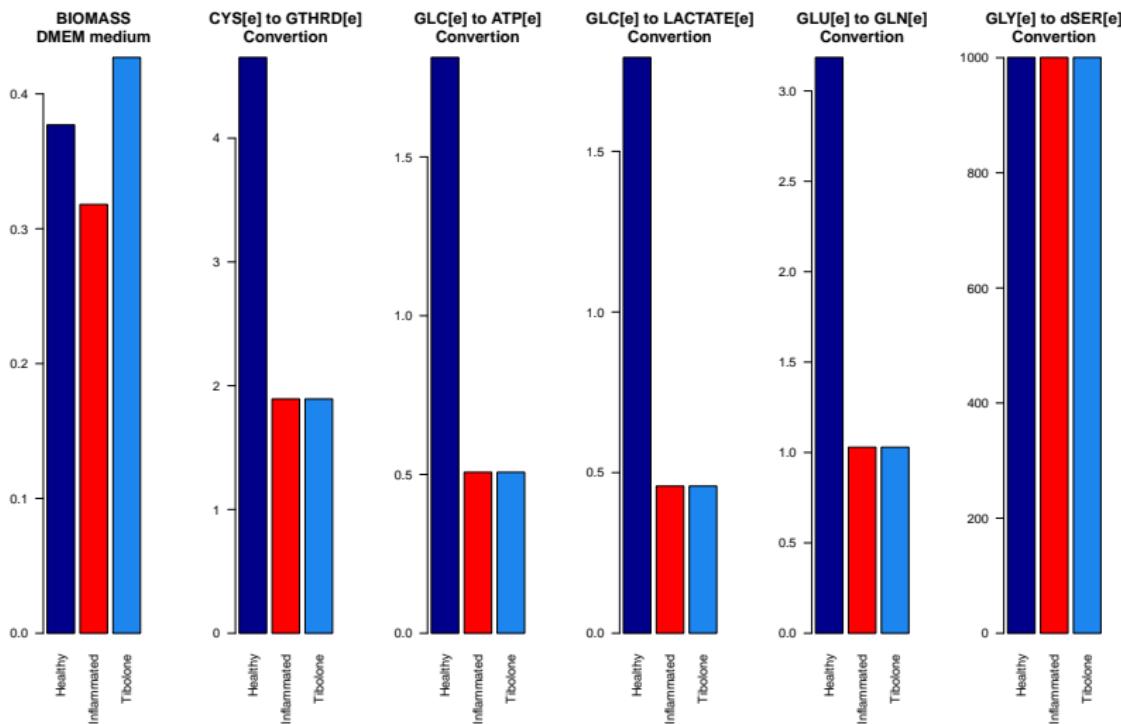
Inflammation Related Metabolic Changes in Astrocytes



Gliotransmitters Release Rate

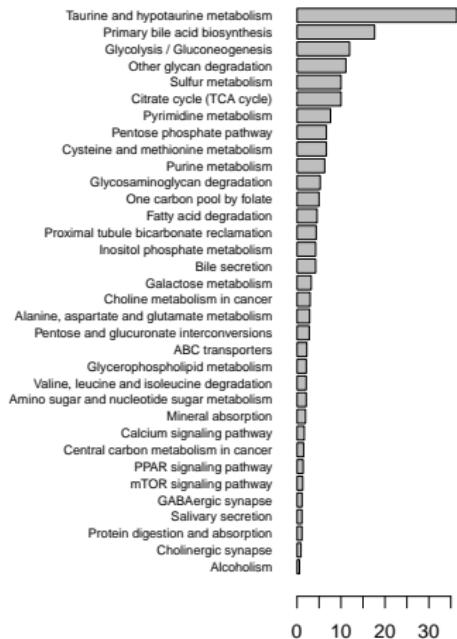


Tibolone Effects in Inflamed Astrocytes

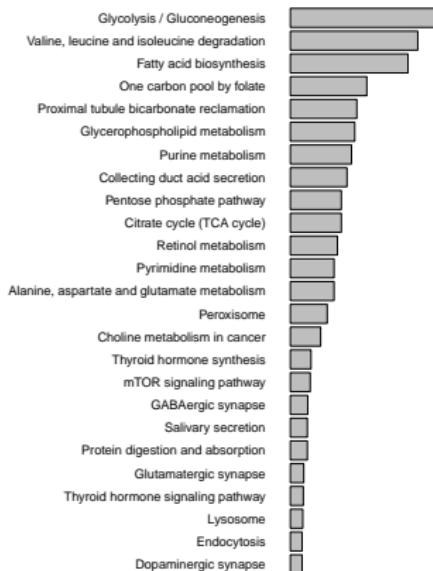


Tibolone Metabolic Changes in Inflamed Astrocytes

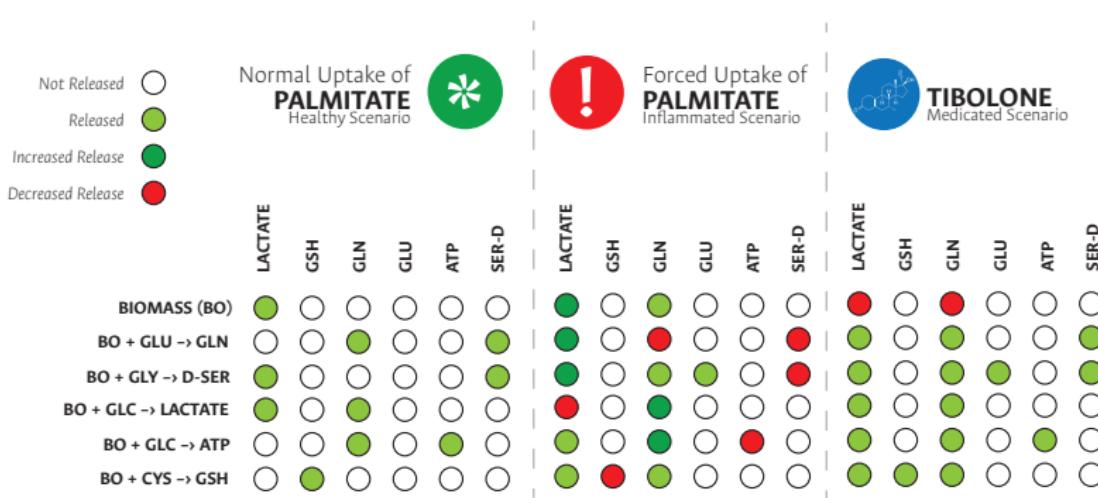
Pathway % Activation



Pathway % Inactivation



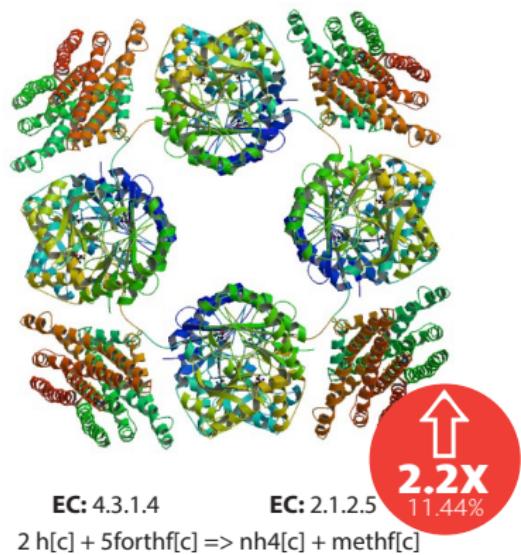
Gliotransmitters Release Rate



ProInflammatory Enzymes

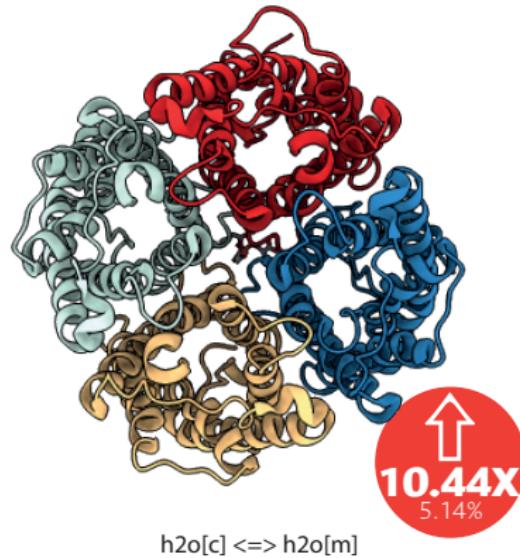
FTCD

FormimidoylTransferase CycloDeaminase



H2Otm

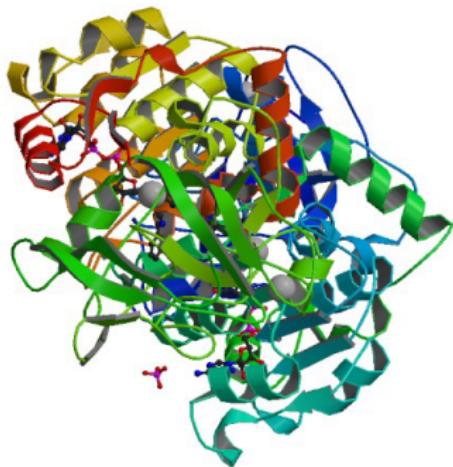
H2O Transport Mitochondrial



Tibolone Related Enzymes

r0739

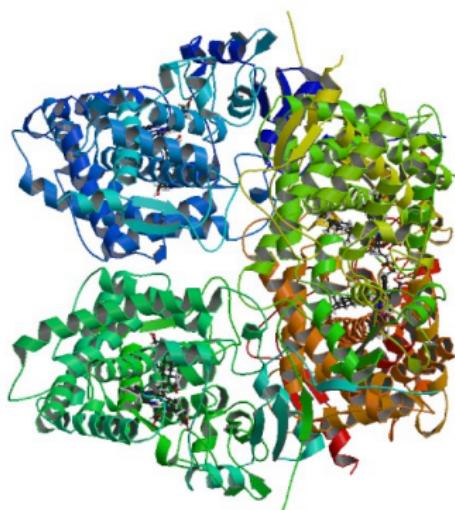
Alcohol Dehydrogenase 1 - 7



EC: 1.1.1.1

**REM1804m | REM1807m**

Cytochrome P450 Family 27 Subfamily A Member 1



EC:1.14.15.15



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

ICGEB Course on Bioinformatics and Computational Neuroscience



Bogotá, Colombia
Short Talk

This study is under development at the:



Bioinformatics and Computational Systems Biology Lab

Institute for Genetics - Universidad Nacional de Colombia

CONTACT:

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Andrés Pinzón PhD
ampinzonv@unal.edu.co