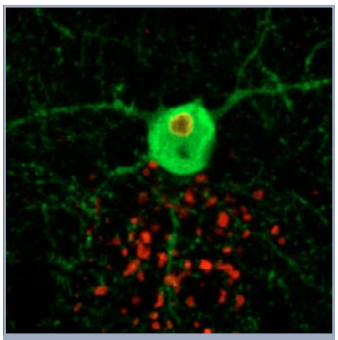
Research Programmes

# MOLECULAR MEDICINE

## Joan J. Guinovart: Metabolic Engineering and Diabetes

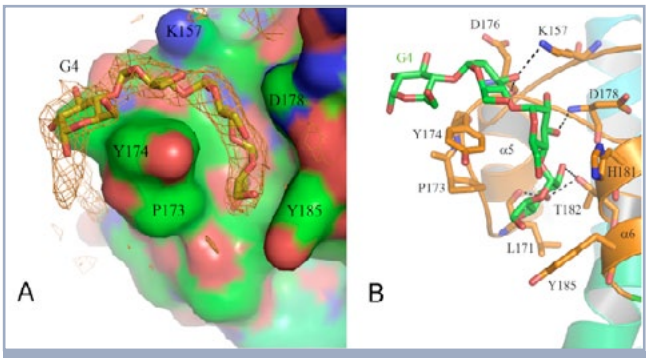
### Highlights

- Mice lacking the malin gene show progressive accumulation of Lafora bodies, loss of parvalbumin-positive hippocampal neurons and brain function deficits.
- We have generated new mouse and *Drosophila* transgenic models in order to study the impact of glycogen over-accumulation or glycogen depletion on specific tissues. The role of glycogen as a metabolic sensor and glycogen-mediated neurodegeneration are currently being studied using these models.



Author: Jordi Vallès Ortega, PhD

Interneuron obtained from an engineered mouse lacking the malin gene (in green) and showing the accumulation of Lafora bodies (in red). Note the presence of a large polyglucosan body in the soma of the neuron and of several other aggregates associated to the neuronal processes.




Author: Adelaida Díaz Vilchis, PhD

In the search for potential modulators of glycogen synthase, the crystal structure of monomeric PaGS has been obtained. This structure reveals the existence of a high affinity glycogen binding site, shown in the figure with surface (A) or ribbon (B) representations. Maltotetraose (shown as sticks) occupies the glycogen binding site by curling around the Y174 residue, and makes hydrogen bonds with K157, L171, D178 and T182.

### Group Members

**Group Leader**

Joan J. Guinovart

**Research Associates**

Joaquim Calbó
Maria Del Mar García

**Postdoctoral Fellows**

Adelaida Díaz Vilchis
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**PhD Students**

Óscar Blanco
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**Research Assistant**

Anna Adrover

**Lab Technicians**

Manuel Gris
Emma Veza

**Administrative Assistants**

Carolina Sánchez

- Restoration of hepatic glycogen deposition by transduction of a constitutively active liver glycogen synthase mutant reduces hyperglycemia, hyperphagia and the expression of gluconeogenic enzymes in STZ-diabetic rats.
- The processivity and subcellular localization of glycogen synthase depend on a non-catalytic high affinity glycogen-binding site. We have structurally and biochemically characterized a novel glycogen-binding motif in glycogen synthase.

## Publications

- Valles-Ortega J, Duran J, Garcia-Rocha M, Bosch C, Saez I, Pujadas L, Serafin A, Cañas X, Soriano E, Delgado-García JM, Gruart A and Guinovart JJ.
  **Neurodegeneration and functional impairments associated with glycogen synthase accumulation in a mouse model of Lafora disease**
  EMBO Mol Med, **3**, 1-15 (2011)
- Ros S, García-Rocha M, Calbó J and Guinovart JJ.
  **Restoration of hepatic glycogen deposition reduces hyperglycaemia, hyperphagia and gluconeogenic enzymes in a streptozotocin-induced model of diabetes in rats**
  Diabetologia, **54**, 2639-48 (2011)
- Fernández-Novell JM, Ballester J, Altirriba J, Ramió-Lluch L, Barberà A, Gomis R, Guinovart JJ and Rodríguez-Gil JE.
  **Glucose and fructose as functional modulators of overall dog, but not boar sperm function**
  Reprod Fert Develop, **23**, 468-80 (2011)
- Borg J, Campos A, Diema C, Omeñaca N, de Oliveira E, Guinovart J and Vilaseca M.
  **Spectral counting assessment of protein dynamic range in cerebrospinal fluid following depletion with plasma-designed immunoaffinity columns**
  Clin Proteomics, **8**, 6 (2011)
- Gómez-Gómez MM, Rodríguez-Fariñas N, Cañas-Montalvo B, Domínguez J, Guinovart J and Cámara-Rica C.
  **Biospeciation of tungsten in the serum of diabetic and healthy rats treated with the antidiabetic agent sodium tungstate**
  Talanta, **84**, 1011-8 (2011)
- Díaz A, Martínez-Pons C, Fita I, Ferrer JC and Guinovart JJ.
  **Processivity and subcellular localization of glycogen synthase depend on a non-catalytic high affinity glycogen-binding site**
  J Biol Chem, **286**, 18505-14 (2011)

## PhD Theses

- Determinants de la unió a glicogen i translocació de la glicogen sintasa. Carles Martinez, Universitat de Barcelona (2011). Thesis director: Joan J. Guinovart. Honors: Cum Laude
- Estudio de la regulación de la glucógeno sintasa hepática por modificación postraduccional. Oscar Blanco Presas, Universitat de Barcelona (2011). Thesis director: Joan J. Guinovart. Honors: Cum Laude
- Modulació transcripcional del metabolisme hepàtic per tungstat de sodi. Laura Nocito Labad, Universitat de Barcelona (2011). Thesis director: Joan J. Guinovart. Honors: Cum Laude

## Research projects

- The dark side of a bright molecule: Determinants of glycogen-induced cell dysfunction. Human HFSP Program Grants, RGP0027/2011 (2011-2014). Principal investigator: Joan J. Guinovart
- Estudio de un nuevo mecanismo de regulación del metabolismo del glucogeno. Análisis de las implicaciones patológicas de la acumulación anómala de polímeros de glucosa. Proyectos de investigación fundamental (BFU2008-00769). Spanish Ministry of Science and Innovation (MICINN). 2009-2011. Principal investigator: Joan J. Guinovart
- Centro de Investigación Biomédica en Red de Diabetes y enfermedades metabólicas asociadas (CIBERDEM), Carlos III Health Institute, CB07-08-0045 (since 2008). Principal investigator: Joan J. Guinovart.
- Enginyeria metabòlica i teràpia de la diabetis, Grups de Recerca reconeguts per la Generalitat de Catalunya 2009-2013 (2009 SGR 1176). Agency for Administration of University and Research Grants (AGAUR). 2009-2013. Principal investigator: Joan J. Guinovart

## Collaborations

- *The use of Drosophila melanogaster as model system for the study of Lafora disease,* Marco Milán, IRB Barcelona (Barcelona, Spain)
- *Electrophysiological effects of the modulation of brain glycogen metabolism,* JM Delgado-Garcia, Agnés Gruart, Universidad Pablo de Olavide (Sevilla, Spain)
- *Glycogen-induced dysfunctions in pancreas and retina and their involvement in the ethiogenesis of diabetes mellitus,* Rafael Simó, Institut de Recerca Hospital Vall d'Hebrón (Barcelona, Spain); Ramon Gomis, IDIBAPS-Hospital Clínic (Barcelona, Spain)
- *Impact of GBE1 defficiency on energy metabolism,* Jerzy Duszynski , Nencki Institute of Experimental Biology (Warsaw, Poland); Adam Godzik, Sanford - Burnham Medical Research Institute (La Jolla, United States)
- *Metabolomic analysis of animal models with deregulated glycogen metabolism,* Xavier Correig, Metabolomics Platform - CIBERDEM (Tarragona, Spain)
- *Molecular dissection of the mechanisms of action of the antidiabetic agent sodium tungstate in skeleton muscle,* Mª Dolores Girón, Rafael Salto, University of Granada (Granada, Spain)
- *Relation between the diabetic syndrome and the key glucose homeostasis enzymes, fructose-1,6-Biphosphatase and glycogen synthase,* Juan Carlos Slebe, Instituto de Bioquímica, Universidad Austral de Chile (Valdivia, Chile)
- *Study of glycogen accumulation in Alzheimer disease,* Isidre Ferrer, Institute of Neuropathology, IDIBELL, Bellvitge University Hospital-ICS (L'Hospitalet de Llobregat, Spain)
- *Study of the actions of sodium tungstate on the ionic homeostasis,* Miguel A Valverde, Pompeu Fabra University (Barcelona, Spain)
- *Study of the alterations of glycogen metabolism in animal models with neurological diseases,* Martí Pumarola, Autonomous University of Barcelona (Barcelona, Spain)
- *Study of the molecular targets and biological actions of sodium tungstate,* José Ramón Murguia, Universidad Politécnica de Valencia (Valencia, Spain)
- *Structural determinants of the activity and regulation of Glycogen Synthase,* Joan Carles Ferrer, University of Barcelona (Barcelona, Spain)

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