

IRB BARCELONA 2010 ANNUAL REPORT

SCIENCE AT IRB BARCELONA

Research Programmes

Molecular Medicine

Joan J Guinovart: Metabolic engineering and diabetes



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Highlights

- New mouse and *Drosophila* transgenic models have been generated 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.
- Restoration of hepatic glycogen deposition by transduction of a constitutively active liver glycogen synthase mutant form improves glucose tolerance in healthy rats and reduces hyperglycemia, hyperphagia and the expression of gluconeogenic enzymes in STZ-diabetic rats.
- 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

- Pescador N, Villar D, Cifuentes D, Garcia-Rocha M, Ortiz-Barahona A, Vazquez S, Ordoñez A, Cuevas Y, Saez-Morales D, Garcia-Bermejo ML, Landazuri MO, Guinovart J and del Peso L. Hypoxia promotes glycogen accumulation through hypoxia inducible factor (HIF)-mediated induction of glycogen synthase 1. *PLoS One*, 5 (3), e9644 (2010)
- Ros S, Zafra D, Valles-Ortega J, García-Rocha M, Forrow S, Domínguez J, Calbó J and Guinovart JJ. Hepatic overexpression of a constitutively active form of liver glycogen synthase improves glucose homeostasis. *J Biol Chem*, 285 (48), 37170-7 (2010)

Collaborations

- Characterization of the anti-diabetic and anti-obesity actions of tungstate. Ramon Gomis, IDIBAPS-Hospital Clínic (Barcelona, Spain)
- Effects of glycogen synthase activators on cultured hepatocytes. Andrée Olivier, Hoffman-LaRoche (Nutley, New Jersey, United States)
- 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)
- Histological analysis of the alterations in the neuronal glycogen metabolism in neurological disease. Teresa Ribalta, Hospital Clínic de Barcelona (Barcelona, Spain)
- *In silico* design of modulators of the glycogen synthase activity. Modesto Orozco, IRB Barcelona (Barcelona, Spain)
- Mechanism of action of anti-hyperglycaemic compounds and development of *in vitro* methods for screening mode of action. Lorraine Agius, School of Clinical Medical Sciences-Diabetes, The Medical School (Newcastle, United Kingdom)
- Molecular basis of Lafora disease. Pascual Sanz, Instituto de Biomedicina de Valencia, CSIC (Valencia, Spain); Santiago Rodríguez de Córdoba, Centro de Investigaciones Biológicas, CSIC (Madrid, Spain)
- Molecular dissection of the mechanisms of action of the antidiabetic agent sodium tungstate in skeletal muscle. M^a Dolores Girón, University of Granada (Granada, Spain); 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 hypoxia and glycogen accumulation. Luis del Peso, Instituto de Investigaciones Biomédicas-CSIC (Madrid, Spain)
- Study of the actions of sodium tungstate on the ionic homeostasis. Miguel A Valverde, Pompeu Fabra University (Barcelona, Spain)
- Study of the alterations in glycogen metabolism associated with colon cancer. Santiago Ramón y Cajal, Institut de Recerca Hospital Vall d'Hebrón (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 Murguía, Universidad Politécnica de Valencia (Valencia, Spain)
- Study of the proteomic alterations induced by tungstate treatment of diabetic animals. Carmen Cámara, Universidad Complutense de Madrid (Madrid, Spain)
- The use of *Drosophila melanogaster* as model system for the study of Lafora disease. Marco Milán, IRB Barcelona (Barcelona, Spain)

Research projects

- Actividades Comité IUBMB, Spanish Ministry of Science and Innovation (MICINN), ACI2008-0741, (2009-2010). 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
- Estudio de un nuevo mecanismo de regulacion del metabolismo del glucogeno. Análisis de las implicaciones patologicas de la acumulacion anomala de polimeros de glucosa. Proyectos de investigación fundamental (BFU2008-00769). Spanish Ministry of Science and Innovation (MICINN). 2009-2011. Principal investigator: Joan J Guinovart
- Mejora de la predicción traslacional de los ensayos de seguridad no clínica al hombre. "MELIUS". Cénit (Noscira, S.A). Centro de Desarrollo tecnológico Industrial (CDTI). Principal investigator: Joan J Guinovart
- Centro de Investigación Biomédica en Red de Diabetes y enfermedades metabólicas asociadas (CIBERDEM), Carlos III Health Institute, CBO7-08-0045 (since 2008). Principal investigator: Joan J Guinovart.
- Nuevos fármacos y dianas para el tratamiento de diabetes mellitus. Fundación Marcelino Botín. 2006-2010. Principal investigator: Joan J Guinovart
- Hoffmann - La Roche Inc., (2009-2010). Principal investigator: Joan J Guinovart