ÁREA: NEUROCIENCIAS

Grupos:

Grupo de Neurología

Responsable: José M. Serratosa Fernández
IP: Marina Sánchez García
Investigación: Básica y Clínica

Grupo de Psiquiatría y Salud Mental

Responsable: Enrique Baca García
Investigación: Clínica

Grupo de Señalización Mitocondrial del Calcio

Responsable: Jorgina Satrústegui Gil-Delgado
Investigación: Básica

ÁREA: NEUROCIENCIAS/Grupo Neurología

1. Esclerosis múltiple

   Ponente: Irene Moreno

2. Enfermedad de Huntington

   Ponente: Pedro García Ruiz-Espiga

3. Enfermedad de Lafora

   Ponente: José María Serratosa

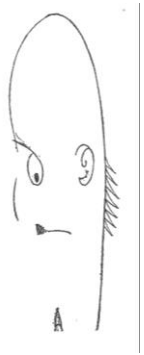
4. Correlaciones clínico-genéticas en demencias familiares

   Ponente: Estrella Gómez Tortosa

New therapeutic strategies for the treatment of Lafora disease

José M Serratosa, Marina Sánchez, Daniel Fernández Burgos, Luis Zafra, Nerea Iglesias, Beatriz González Giráldez, María Machío, Gema Sánchez

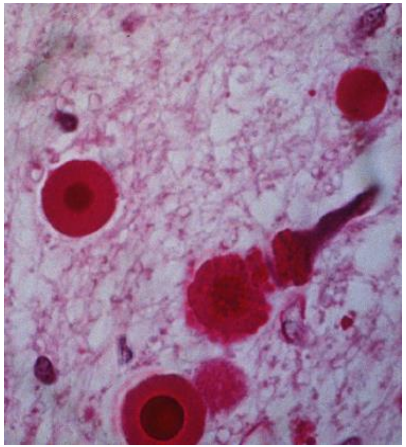
Grupo de Neurología/Epilepsias
jmserratosa@fjd.es
Ext 3451

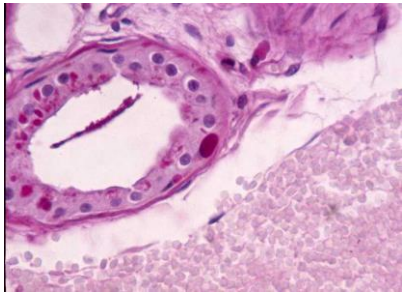


III REUNIÓN ANUAL DEL ÁREA DE NEUROCIENCIAS DEL IIS-FJD
8 de junio de 2021

PME of Lafora

- Age at onset 10–18 years
- **Progressive –** neurological deterioration
  - Rapidly progressive dementia
  - Ataxia, agnosia, apraxia, aphasia
- **Myoclonus –** asymmetric, arrhythmic
- **Epilepsy –** GTC, myoclonic, absences, tonic
- Severe incapacity and death in <10 years
- Pathology: Lafora bodies
- **Genetics: *EPM2A*, *EPM2B***





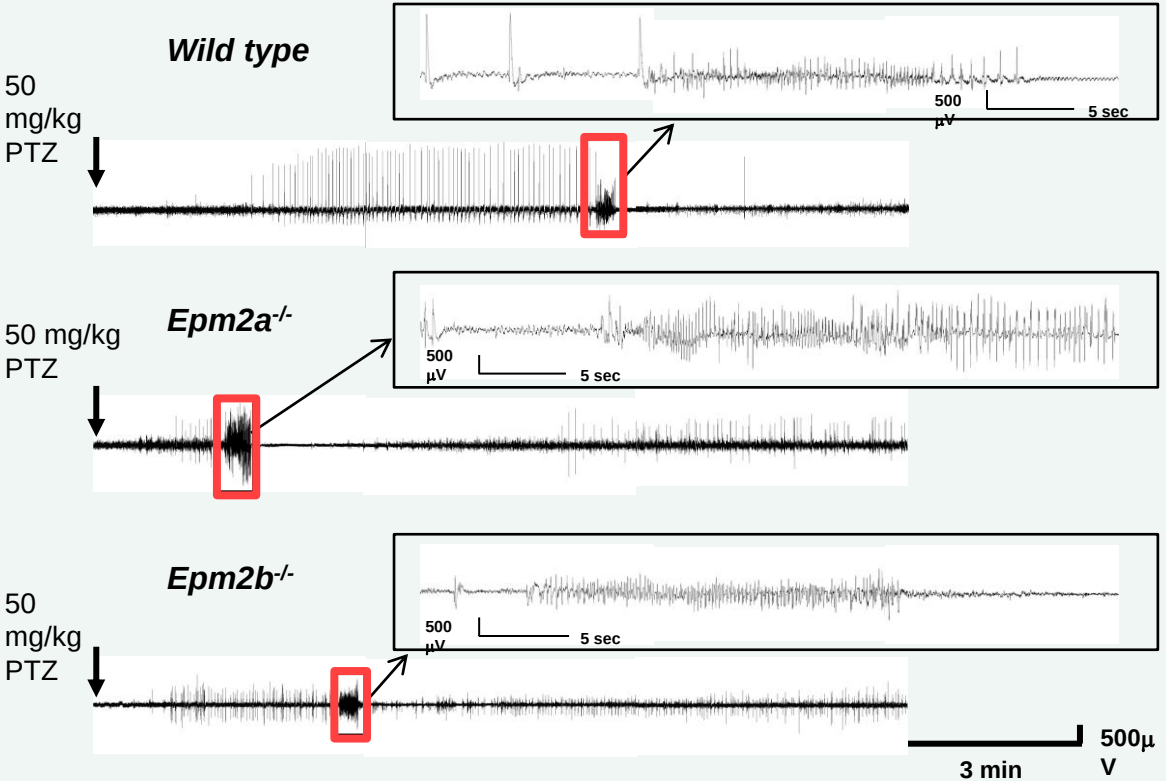
Mouse models of LD: *Epm2a* and *Epm2b knock-outs*

- Abundant Lafora bodies in the CNS and other tissues
- Altered motor activity, impaired motor coordination and dyskinesias
- Important cognitive deficits
- Impaired autophagy and oxidative stress
- Increased sensitivity to PTZ induced seizures

García Cabrero et al, 2014
Berthier et al, 2015
Sánchez-Elexpuru et al, 2017

Epm2a and *Epm2b* ko mice present longer GTC sz + less latency

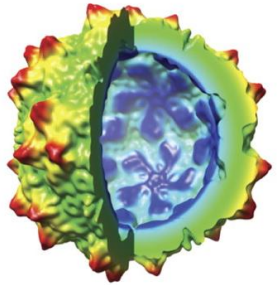
- *Epm2a*$^{-/-}$ and *Epm2b*$^{-/-}$ models present GTC seizures with particular patterns of discharges



New therapeutic strategies

- 1. Gene therapy
- 2. Antisense oligonucleotides (ASOs)
- 3. Antibody-enzyme fusions
- 4. Small molecules
  - Repurposed drugs
  - Newly designed drugs

Gene therapy

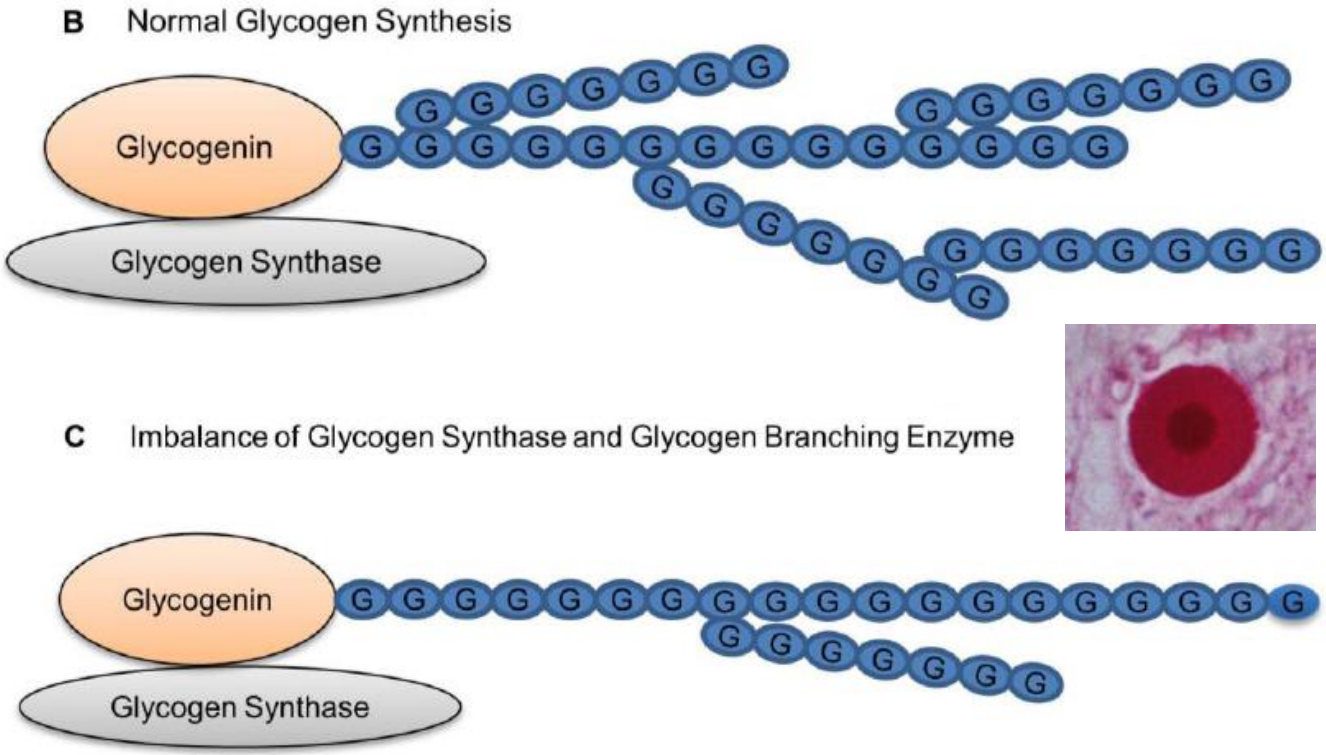


Gene therapy

Proyecto financiado por:
Fundación Tatiana Pérez de Guzmán el Bueno

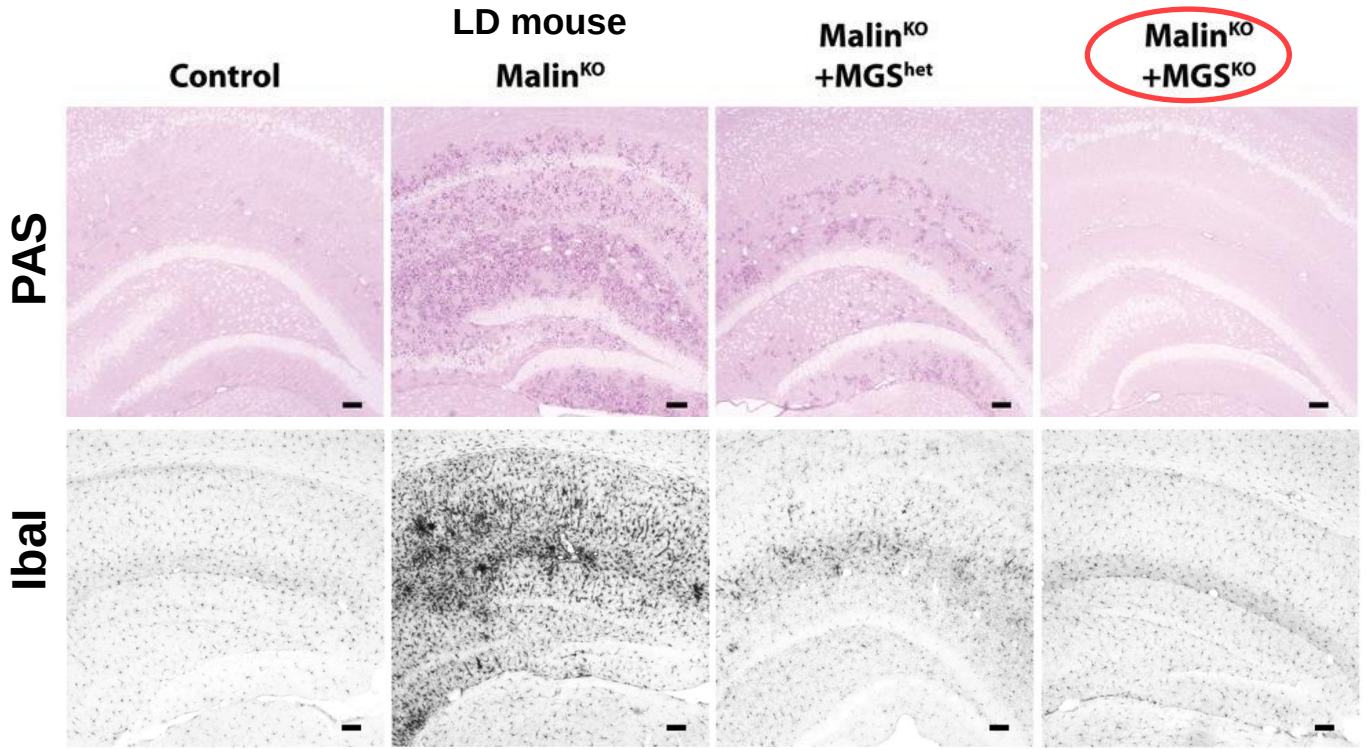
- AAV2/9-CAG vector containing laforin and malin (colaboration with Miguel Chillón – Viral Vector Unit UAB)
- Intracerebroventricular injection of Laforin KO mice at 3 months ─> histologic, epilepsy and behavioral characterization at 6 and 12 months

Lafora disease: Imbalance of GS and BE and synthesis of abnormal of abnormal glycogen



From Phan, 2014

Underexpression of glycogen synthase stops LB formation and neurodegeneration



MGS = muscle glycogen synthase

Duran, et al. *Hum Mol Genet.* 2014

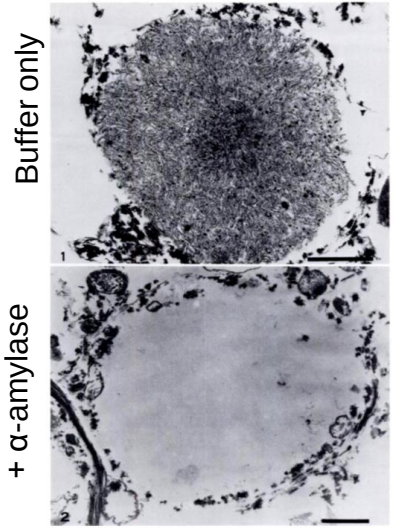
Antisense oligonucleotides (ASOs) for LD

- ASO knock-down of glycogen synthase
  - Prevents Lafora body formation if given early
  - Stops Lafora body formation in later stages
  - LECI and Ionis Pharmaceutical preparing clinical trial

Ahonen et al, Brain 2021

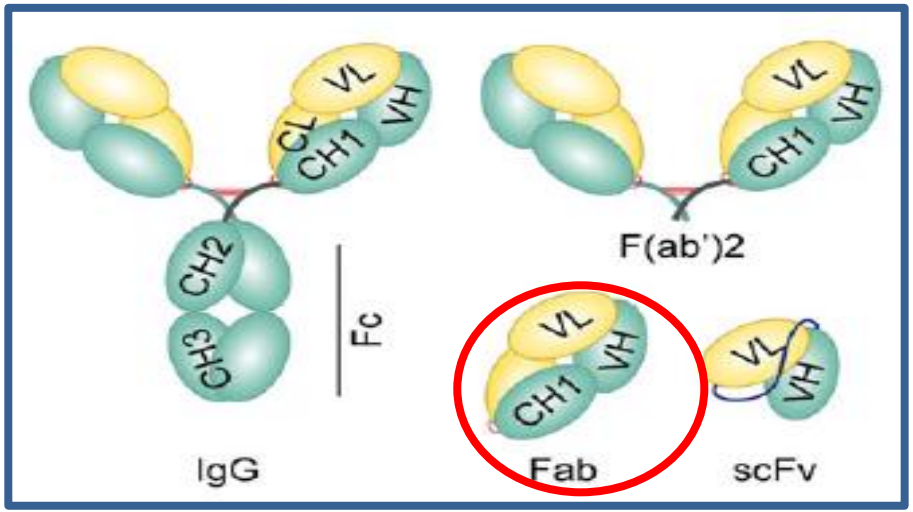
Antibody-enzyme fusion (AEF) platform

Lafora body
(fixed human tissue)



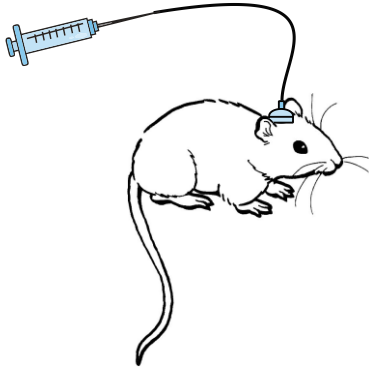
Nikaido et al. 1971. *J Histochem Cytochem*.

valerion



Antibody-enzyme fusion (AEF) treatment

Intracerebroventricular (ICV) injection



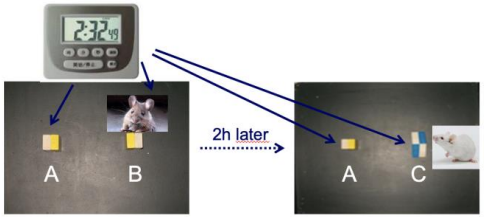
Infusion of VAL-1221 (0.12 mg) or PBS via ICV single injection or via ICV with continuous infusion (osmotic pump) 9 month old laforin KO mice

1 week

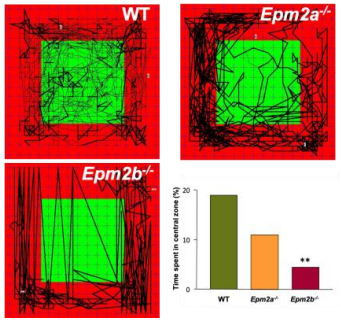
Alzet osmotic pump

Pentylenetetrazol (PTZ)

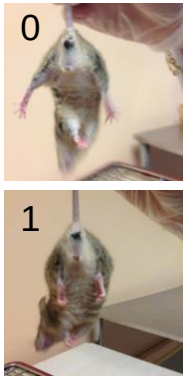
Memory: Object recognition task (ORT)



Anxiety: Actimeter & Actitrack



Abnormal postures: tail suspension tail (TST)



Neuropathology

Treatment of *Epm2a* and *Epm2b* mice with metformin

- *Epm2b*$^{-/-}$ mice show decreased number of Lafora bodies
- Improved motor activity and dyskinesias
- Reduced sensitivity of *Epm2b*$^{-/-}$ mice to convulsant PTZ

Berthier et al, 2015
Sanchez-Elexpuru et al, 2017

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 January 2017
EMA/741007/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

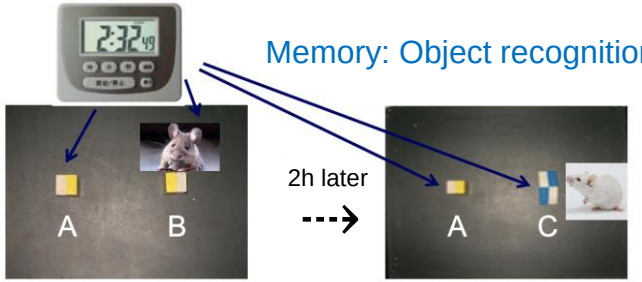
Metformin for the treatment of progressive myoclonic epilepsy type 2 (Lafora disease)

On 12 December 2016, orphan designation (EU/3/16/1803) was granted by the European Commission to Centro de Investigación Biomédica en Red (CIBER), Spain, for metformin for the treatment of progressive myoclonic epilepsy type 2 (Lafora disease).

Question: Is early treatment worth it?

- Is early treatment more effective than later treatment?
  - We treated *Epm2a* and *Epm2b* KO mice with 12 mM metformin since conception
  - We evaluated mice at 3, 6 and 12 months
    - Lafora bodies
    - Behavioral tests
    - Sensitivity to PTZ

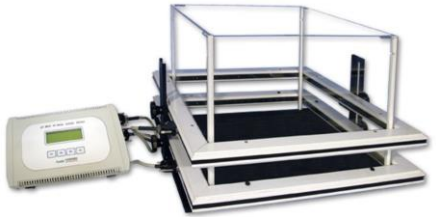
Behavioral, histological and neuronal hyperexcitability analysis



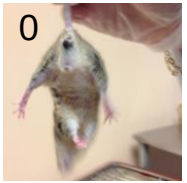
Memory: Object recognition task (ORT)

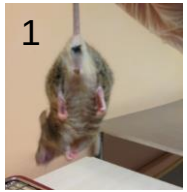
$DI = t_C - t_A / t_T$

Spontaneous movement: Actimeter



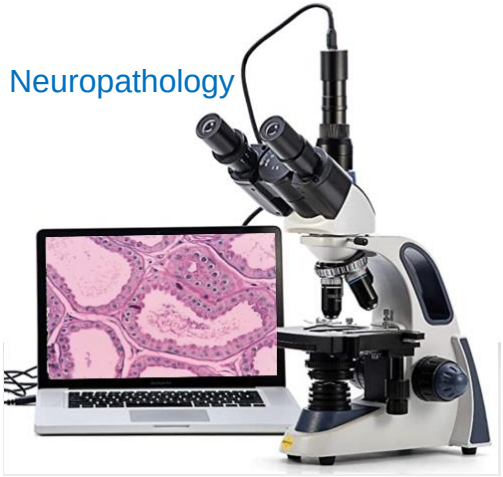
Abnormal postures: tail suspension tail (TST)





Motor coordination: Rotarod

Neuropathology



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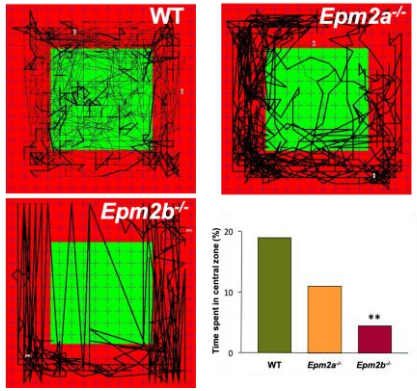


Pentylenetetrazol (PTZ)

Early-MET in 12-month-old LD mice

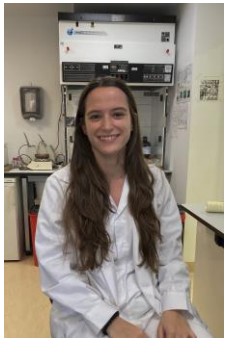
- Decreases neuronal hyperexcitability in LF and ML mice
- Improves spontaneous movement and motor coordination behavior
- Abolishes hindlimb clasping
- Avoids memory decline in LD mice
- Prevents neuronal loss and astrocytosis

Genetic Epilepsies Group at Madrid FJD

José M. Serratosa, MD, PhD

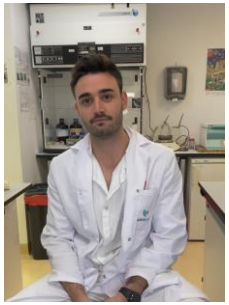
Daniel F. Burgos, MSc

Gema Sánchez-Martín, Tech

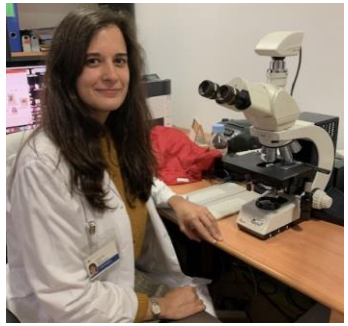


Nerea Iglesias Cabeza, MSc

Marina P. Sánchez, PhD



Luiz Zafra-Puerta, MSc



María Machío-Castellón, MD

Juan González-Fernández, PhD

Beatriz G. Giráldez, MD

Hospital Universitario Fundación Jiménez Díaz

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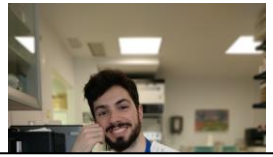
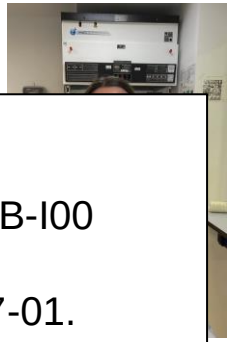
Genetic Epilepsies Group at Madrid FJD

José M. Serra





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Beatriz G. Giráldez, MD

Marina P. Sánchez, PhD

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