

Genome



GENAME

Defining targets for therapeutics in Spinal Muscular Atrophy

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Genoma España



Fun⁰AME
Fundación Atrofia Muscular Espinal

Summary

A strong research infrastructure may improve and accelerate basic science to the clinical level. Translational research in neuromuscular disorders has proven to be a powerful process that drives the clinical research machinery. With the main financial support from Genoma España (a Spanish government agency) and [FUNDAME](#) (Spanish SMA foundation) we established in 2007 a collaborative project ([GENAME](#)) involving a wide spectrum of groups from basic neurobiology to clinical care pointing to a concerted action to generate SMA translational research in Spain. The main goal was to provide the groundwork for identification of promising targets that will allow the treatment of the disease. This project established a collaboration between 16 Spanish investigators, 15 based in Spanish Centres and one in the University of London. We aimed to perform a multidisciplinary approach in four main areas: clinical, genetic-proteomics, neurobiology and therapeutics of the disease. Clinical aspects included the creation of a National Registry of Patients, biobanking, natural history, early intervention and the validation of outcome measures. The first accomplished objective was the genetic characterisation of all available Spanish SMA patients (Alias et al., 2009). In addition, genetic influences that affect SMN protein abundance or its role in the motor neuron have been approached by genomic, transcriptomic, metabolomic and proteomic studies. A thorough neurobiology approach of the disease studying the available animal models was also investigated. Finally, novel experimental therapies have been developed and evaluated.

Participants

COORDINATOR

Group 1. Dr. Eduardo Tizzano. *Servicio de Genética e Institut de Recerca Hospital Santa Creu i Sant Pau, Barcelona.*

CLINICAL

Group 6. Dr. Jaume Colomer. *Servei de Neurologia, Hospital Sant Joan de Déu, Barcelona*

Group 7. Dr. Anna Febrer. *Servei de Rehabilitación, Hospital Sant Joan de Deu, Barcelona*

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Group 4. Dr. Concepción Hernández, *Unidad de Genética Molecular, Hospital Ramón y Cajal , Madrid*

METABOLOMICS

Group 5. Dr. Teresa Pámpols, *IBC, Hospital Clínic. Barcelona.*

PROTEOMICS

Group 9. Dr. Joaquín Abián. *CSIC/UAB Laboratorio de Proteómica, Barcelona*

NEUROBIOLOGY

Group 8. Dr. Manel Roig. *Grupo Patología Neuromuscular, Neurología Infantil, Hospital Vall d'Hebron, Barcelona*

Group 10. Dr. Rosa Soler. *Unidad de Señalización. Departamento de Ciencias Médicas Básicas, Universitat de Lleida*

Group 11. Dr. Josep Esquerda. *Unidad de Neurobiología. Departamento de Ciencias Médicas Básicas, Universitat de Lleida*

Group 12. Dr. Jerònia Lladó. *Unidad de Neurobiología. Universidad de Islas Baleares*

Group 13. Dr. Lucía Tabares, *Departamento de Fisiología. Facultad de Medicina. Universidad de Sevilla*

NOVEL THERAPIES

Group 14. [Dr. Rafael Yáñez.](#) *School of Biological Sciences, Royal Holloway, University of London, London*

Group 15. Dr. Rosario Osta. *Facultad de Veterinaria, Instituto Aragonés Ciencias de la Salud, Zaragoza*

Group 16. Dr. José Aguilera. *Departamento de Bioquímica y Biología Celular, UAB, Barcelona*

A total of 76 people were involved in the project full- or part-time.

CLINICAL MILESTONES

Neurophysiological studies and validation of motor function scales was generated in 60 patients with SMA followed by two groups (G6 and G7) in one centre.

Biological markers and the metabolic profile of these patients gathered information that is potentially useful for future clinical trials of the disease (G1 and G5).

A professional Registry and a Biobank are available.

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GENETIC AND PROTEIN MILESTONES

Compilation of data by the four main genetic diagnosis centers (G1–G4) has enabled the collection of very important information about molecular epidemiology and pathology of the SMN1 in almost 750 Spanish SMA patients. Five-hundred thirty one (531) of these patients were analyzed with novel genomic techniques to characterize the structure of the SMA locus and SMN2 copy number

Transcriptomic (G1) and proteomic studies (G9) in discordant siblings discovered a few genes and proteins that may be phenotypic modifiers of the disease.

Studies of Plastin in discordant siblings and c.859C>G variant in SMN2

Treatment of cells of patients with known drugs that upregulate the SMN2 gene indicate that there is inter- and inpatient variability in the response.

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NEUROBIOLOGY MILESTONES (1)

Human studies focusing on muscle have come up with interesting results, pointing to a delay of muscle maturation during human development and impairment of the neuromuscular junction in SMA fetuses (G1).

New methods such as microdissection of hypertrophic-atrophic fibers in muscle and motor neurons of the anterior horn have been developed and expression of different genes was investigated (G8).

Motor neurons of the anterior horn of mice were isolated, cultured and transfected and a SMN knock-down model has been developed (G10).

Compelling results were obtained by immunohistochemical and ultrastructure analysis of muscle fibers, endplates and synapses supporting the hypothesis of primary involvement of muscle and a defect-dysfunction in the neuromuscular junction in mice with SMA (G11).

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NEUROBIOLOGY MILESTONES (2)

Organotypic cultures were investigated for the first time SMA mouse models with interesting results on the SMN basal expression.

Transfection studies are also being conducted to analyze the effect of decreasing SMN levels.

Neuro-inflammation was another challenging area of work that was also investigated in this model (G12).

Electrophysiological studies showed that mutant terminals secrete neurotransmitter in a synchronous way, and that secretion is depressed in the most distal terminals innervating the caudal part of the investigated muscles (G13).



THErapy MILESTONES

The neurotrophic properties of the Hc-TeTx was evaluated as a potential therapeutic agent to investigate in the SMA models (G15-G16).

Different models of lentiviruses constructions (G14) were generated to conduct transfection studies in vitro (motor neuron, organotypic - spinal cord) and in vivo (mice).

All these groups worked in close collaboration and interaction, pooling material /skills/ knowledge/information/expertise for the benefit of the project

Gename

