Proyectos de Investigación Aplicada Colaborativa:

*Discovery and development of pharmaceuticals efficacious for amyotrophic lateral sclerosis*

Olga Genilloud, Scientific Director

Fundación MEDINA
Fundación MEDINA
Parque Tecnológico Ciencias de la Salud, Granada
Fundación MEDINA

— Not-profit Research Center for the discovery of new compounds and innovative therapies for unmet medical needs.

— Public-private partnership established in the Health Sciences Technological Park (PTS) of Granada among:
  — Merck Sharp and Dohme de España S.A.
  — Junta de Andalucía (Ministry of Economy, Science and Innovation & Ministry of Health)
  — University of Granada

— Independent legal entity

— Technology transfer from the former Basic Research Center of MSD de España S.A. (CIBE)
  — More than 50 years experience in drug discovery from microbial natural products
  — Reference Center for Preclinical Evaluation of drug candidates.
2300 m² of laboratory space
Resources and facilities

- Microbial collections
- HTS screening platform
- Preclinical safety platform
- Natural Products Libraries
Fundación MEDINA

- **Multidisciplinary organization** with research expertise in industry, academia and health research institutes.

- **Mixed Institute**: Objective to integrate in the medium term research groups from the University and the Health Sciences Institutes in Andalucía.

- Public-private characteristics: best position for development of **Scientific Collaboration Opportunities** with Academia, the Biotech sector and Big Pharma.

- **Research Funding opportunities**: from regional, national and international granting agencies.

- **Mixed business model** for contract research agreement and screening services.
**Fundación MEDINA Activities**

**Research:**
- Drug Discovery from microbial Natural Products
- Supporting Natural Products Research programs

**Services and Research Contracts (CRO):**
- HTS Screening for Drug Discovery from NPs
- Safety profiling for preclinical evaluation of drug candidates

**Advanced Therapies:**
- Development of GMP facilities for production of viral vectors for ex vivo and in vivo gene therapies

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**Fundación Centro de Excelencia en Investigación de Medicamentos Innovadores en Andalucía**
MEDINA Research Activities: Drug Discovery
Drug Discovery at Fundación MEDINA

- Early discovery
- Hit to lead
- Preclinical
- Phase I
- Phase II
- Phase III

Partners (Academia)

MEDINA

Partners (Risk Sharing)

Partners (Licensing)
Therapeutic Areas in MEDINA Drug Discovery

- Infectious Diseases
  - Antibiotics
  - Gram negative
  - Tuberculosis
  - Antifungals
  - Aspergillosis

- Parasitic Diseases
  - Malaria
  - Leishmaniasis
  - Tripanosomiasis

- Oncology
  - Kidney
  - Breast
  - Pancreas
  - Lung

- Rare Diseases
  - Neurodegenerative Rare Diseases
  - Amyotrophic Lateral Sclerosis
  - Neuroprotection

- Infectious Diseases
- Parasitic Diseases
- Oncology
- Rare Diseases
Public-Private partnership model in Rare Diseases Drug Discovery

• Collaboration in R&D programs to deal with unmet needs in Rare diseases
• Collaboration Agreement with CIBERER
• Amyotrophic Lateral Sclerosis:
  – Proyecto de investigación aplicada: “Discovery and development of pharmaceuticals efficacious for amyotrophic lateral sclerosis”

Partners:
  – Fundación MEDINA
  – Instituto Química Médica, CSIC
  – Fac. CC. Biológicas, Univ. Complutense.
Amyotrophic Lateral Sclerosis

• Progressive neurological disease of unknown origin
• Motor neuron disease: gradual degeneration and death of motor neurons in brain and spinal cord, resulting in muscle weakness and atrophy.
• Rare disease: prevalence 5,2/100,000.
• Affects adults (average age onset 50 years)
• Sporadic ALS is the most common form of the pathology (only 10% of familial cases (SOD G93A)).
• Few symptomatic treatments available (Riluzole)
• Less than 25 different therapeutic approaches in clinical development (clinical.trials.gov)
Therapeutic approaches to ALS

Neuropathological signatures of ALS:

- **up-regulation** of glycogen synthase kinase 3 (**GSK-3**) in brain and spinal cord: potential pathogenic mechanisms of ALS, via neurofilament phosphorylation, axonal transport regulation and apoptotic pathways

- **mitochondrial dysfunction** of motor neurons: oxidative stress and accumulation of reactive oxygen species (ROS)

- **hyperphosphorylated**, ubiquitinated and N-terminally truncated TAR DNA binding protein (**TDP-43**) in the cytoplasm of motor neurons: involvement of **Casein kinase CK-1**

→ Potential role of **ROS, GSK-3 β** and **Casein-Kinase 1 CK-1** in the molecular pathways activation that induce the motor neuron death in ALS.
Collaborative and Applied Research in ALS:
*Discovery and development of pharmaceuticals efficacious for amyotrophic lateral sclerosis*

**Fundación MEDINA**
Dr. F. Vicente

**Instituto Química Médica, CSIC**
Dr. A. Martínez

**CC. Biológicas, U. Complutense**
Dr. R.M. Arahuetes
Dr. M. Solas

- Synthetic libraries
- Modeling
- Target based assays

- NPs libraries
- HTS screening
- NPs chemistry
- Preclinical safety

- Sporadic murine animal model
- Cell assays
Discovery and development of pharmaceuticals efficacious for Amyotrophic Lateral Sclerosis

Objectives:

**HTS**: High throughput screening of Natural Products against targets associated to ALS

**Medicinal chemistry of novel synthetic compounds**

**Preclinical safety studies of novel compounds effective in ALS**

**Characterization and evaluation of novel compounds in a sporadic animal model of ALS**
Mode of action and preclinical studies of new inhibitors

Medina NPs libraries screened

Families of active NPs:

Selected Compounds: antioxidants and GSK3 inhibitors

Synthetic compounds and med chem libraries

Preclinical safety studies:
Cytotoxicity on 20 cell lines
Metabolism:
• CYP450 interaction
• Drug metabolism and stability
Neurotoxicity: Serotonin and dopamine receptors
Cardiotoxicity: Na⁺, K⁺, Ca²⁺ Channels

Mode of action on neural cell lines:
Mitochondrial studies
Neuroprotection
Apoptosis
Cell viability

High Content Screening Technologies

Murine ALS model
Validation in animal model
Neuroprotection: Cell viability assay

MTT test of MDN GSK3 inhibitor in differentiated PC12 cells

Cell death by L-BMAA

[µM] MDN treatment

1,56 3,13 6,25 12,50

L-BMAA
MDN + L-BMAA
Project outcome

○ Drug discovery from NPs and synthetic libraries:
  • 40,000 extracts screened against GSK3 and ROS:
    – 5 families of new compounds identified from natural products: antioxidant inhibitors of GSK3
    – Two patent applications in preparation with support of Genoma España
  • Med Chem of synthetic compounds:
    – Novel allosteric inhibitors for GSK3 from at least three different chemical series
    – New patent applications

○ Sporadic rodent model of ALS:
  • Development of animal model, patent in preparation
Future prospects for the Consortium

- Develop solid technological platform:
  - **Innovative drug candidates** (natural products and synthetics)
    - allosteric GSK-3 inhibitors with good ADME-tox profiles and efficacy on sporadic ALS model.
    - CK-1 inhibitors and their therapeutic potential in different models of ALS (CK-1, new emerging target)
  - High-content cell-based screening assay platform (MOA)
  - Unique sporadic murine model for ALS: final validation

- Obtain first in class protein kinase inhibitors for different motoneuron diseases (ALS, AD, dementia)

- **New proposal**: Proyecto Coordinado Plan Nacional 2012
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- **First public-private Drug Discovery Research Platform** in Spain allowing **collaborative R&D and technology transfer** between industry and academia.

- **Open drug discovery facilities** available for public and industrial high throughput screening in Spain (Spanish Screening Network: [www.medicamentos-innovadores.org](http://www.medicamentos-innovadores.org)) and largest natural products libraries.

- **Multidisciplinary organization** with scientific staff with research expertise in industry, academia and health institutes.

- **Major focus on development of new therapies for unmet medical needs**

- Privileged position for development of **Scientific Collaboration Opportunities** with International Academic Institutions, Biotech and Pharmaceutical Companies.
Research Collaborations & Agreements at Fundación MEDINA
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