IRB Barcelona Translational Research and Innovation Programme
TRIP-Clinics

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Proposal Title: Novel therapies in pediatric neurodegeneration with energy metabolism dysfunction: MENCIA LAB.

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(add more if required)

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Research on animals and human subjects

	YES	NO	N/A
1. This proposal includes animal research	x		
2. The proposed animal research has been approved by the pertinent Committee		x	
3. This proposal includes human subjects or human tissue/cells	x		
4. The proposed research on human subjects or human tissue has been approved by the pertinent Committee		x	

Proposal Title: Novel therapies in pediatric neurodegeneration with energy metabolism dysfunction: MENCIA LAB
Project Leaders: Alejandra Darling & Antonio Zorzano

PROJECT WRITING GUIDELINES

1. ABSTRACT AND SIGNIFICANCE / 300 words

The growing incidence of neurodegenerative diseases represents a huge challenge, and their understanding requires multidisciplinary approaches. Neurodegenerative disorders are heterogeneous and characterised by a progressive loss of neurons leading to the loss of previously acquired motor, sensory and cognitive functions. The mechanisms by which neurodegeneration develops are not well understood, and increasing evidence implicates mitochondrial dysfunction in its development and progression. Unlike the case of neurodegenerative pathologies in adulthood, in pediatric neurology neurodegeneration, the defects are mostly monogenic, and this situation offers a unique opportunity to identify novel neurodegeneration pathways and therapeutic targets.

We propose to create an IRB Clinics Laboratory initially oriented to study the mechanisms that control the synthesis of mitochondrial proteins, and to search for therapies in one neurodegenerative disorder, referred to as COXPD1. This disease is caused by mutations in the nuclear gene GFM1, which encodes the mitochondrial translation elongation factor G1 (EFG1), and it manifests very early after birth with a hepatoencephalopathic clinical picture. There is no treatment for this disease and patients often die during the first months of life.

The approach will involved two distinct strategies:

a) Search for therapies through the screening in human fibroblasts and in bacteria with a library of compounds to rescue the alterations driven by EFG1 mutations, followed by delineation of a preclinical path, and a clinical trial.

b) Search of processes downstream of EFG1 by analysis of mitochondrial and cytosolic translation by ribosome profiling in control or mutant fibroblasts, and identification of RNA-binding proteins and mRNAs in the vicinity of control and diseased fibroblasts.

We propose a transformative research that will change our understanding on the mechanisms that drive neurodegeneration, and will permit the identification of compounds with beneficial activity in cells and mice carrying GFM1 mutations. It will also bring clinical expertise closer to IRB Barcelona.

2. LAY SUMMARY / 300 words

Neurodegenerative diseases show an enhanced incidence, which represents an enormous challenge for our society. Today, it has become clear that the fight against this group of conditions requires multidisciplinary approaches. The definition and diagnosis of neurodegeneration in the pediatric population are harder than in adulthood. Unlike the case of neurodegenerative pathologies in adulthood, in the field of pediatric neurology, defects are mostly defined as due to the participation of a single gene (monogenic), often as a consequence of mutations that affect mitochondria. This situation also offers a unique opportunity to identify new proteins responsible for neurodegeneration and novel ways to treat the disease.

In this proposal we propose the creation of an IRB Clinical Laboratory that we name LAB MENCIA, initially aimed at studying the mechanisms that control the ability of cells to synthesize mitochondrial proteins, and seeking therapies for a neurodegenerative disorder (and also mitochondrial), called COXPD1. This disease is caused by mutations that affect a protein responsible for protein synthesis in the mitochondria, named EFG1. This disease manifests very early after birth, with alterations in brain development, and there are no pharmacological treatments.

The activities to be developed are the following:

a) Search for therapies by means of massive screening tests in human cells and in other cell models in order to improve the alterations caused by the mutant protein EFG1, followed by the development of a preclinical route and design of a clinical trial.

b) Generation of new knowledge that allows the identification of processes that reverse the alterations caused by the mutant protein EFG1.

In short, we propose a transformative research that improves the understanding of neurodegeneration and that identifies compounds with beneficial activity in cells and mice carrying mutations in EFG1. This proposal will also make it possible to bring clinical expertise to IRB Barcelona.

3. *PROJECT DESCRIPTION* / Up to 5 pages

Background

The growing incidence of neurodegenerative diseases is a relevant challenge in our society, and the understanding of this group of conditions requires multidisciplinary and combinatorial approaches. In spite of their great clinical need, there has been little success in developing effective therapies for neurodegenerative diseases. In contrast with the assessment of neurodegeneration in adult neurology in which Alzheimer's and Parkinson's diseases are largely prominent, differential diagnosis in pediatric neurology is challenging, due to differents situations (i.e., the underlying diseases are mostly rare and predominantly genetic with only a few specialized clinical centres having expertise, wider and heterogeneous pathogenetic mechanisms and clinical presentations, the clinical difference between the loss of a previously acquired cerebral function and the delay in the acquisition of specific developmental abilities can be difficult to assess). Unlike the case of different neurodegenerative conditions in adulthood, which most of them are multifactorial, the defects are defined mostly monogenic in pediatric neurology, and this may offer a unique opportunity to study the neurodegeneration pathways.

Mitochondrial dysfunction is thought to play an important role in the mechanism of progression of various neurodegenerative disorders. Disrupted mitochondrial function causes increased production of reactive oxygen species, which is detrimental to neurons and glia[2], thus leading to neuroinflammation, and ultimately to neurodegeneration[1]. A large number of diseases are caused by mutations in nuclear or mitochondrial genes that give rise to defects in oxidative phosphorylation (OXPHOS), and to neurological disorders [3-5].

Our rationale is that by setting the research focus beyond disease condition, and by developing a deep understanding of the underlying mechanisms, this will permit us to propose more efficient therapeutic strategies of use in different neurodegenerative conditions. In this connection, we propose to create an IRB Clinics Laboratory oriented to study the mechanisms that control the capacity of cells to synthesize mitochondrial proteins, and more specifically to search for therapies in one specific mitochondrial disorder, and referred to as combined oxidative phosphorylation deficiency type 1 (COXPD1; OMIM # 609060). COXPD1 is an autosomal recessive multisystem disorder with variable manifestations resulting from a defect in mitochondrial oxidative phosphorylation. The disease is caused by mutations in the nuclear gene GFM1, which encodes for the mitochondrial translation elongation factor G1 (EFG1)[6-8]. The disease manifests itself very early after birth with a hepatoencephalopathic clinical picture and progresses rapidly. Other common clinical traits are feeding difficulties, dystonia, hyper-or hypotonia, brain MRI abnormalities, and liver failure [9-18]. There is no treatment for this disease and patients die during the first months of life, although some cases surviving beyond 6 years of age have been reported. The low number of patients described thus far makes it difficult to identify any correlations between genotype and clinical outcome, although some authors have proposed that the mutation localization in the protein could account for the disease severity [15]. Furthermore, the most common variant described in COXPD1 patients is c.2011C>T causing the missense mutation p.(Arg671Cys), which is also present in most patients with longer survival [11, 12, 15, 19]. Recently, a knock-in mouse for the most common amino acid changes in patients (R671C) has been generated [20]. The compound heterozygous $Gfm1^{R671C/-}$ mouse shows a phenotype that resembles many of the alterations found in COXPD1 patients, and it is a useful model to study hepatoencephalopathy caused by mutations in GFM1 [20].

Specific aims.

Hypothesis. Recent studies in the field of mitochondrial biology, including work performed by members of the proposal, indicate that mitochondrial dysfunction caused by mutations in mitochondrial proteins initiate a

mitochondrial stress response that can adopt various molecular patterns, and whose mechanisms are mostly unknown [21-24]. This propitiates adaptive responses that attempt to bypass the original defects [25, 26].

On the other hand, cells under conditions of a defective mitochondrial protein synthesis synthesis, may also trigger compensatory processes both inside the mitochondria and in its vicinity [27], in order to counteract the primary defect.

In short, our specific hypothesis is that there must be compensatory mechanisms that, if activated efficiently, can ameliorate the deficiencies caused by mutations in the mitochondrial translation elongation factor G1 (EFG1). In this connection, the creation of the IRB Clinics Laboratory aims at studying the mechanisms that boost the ability of cells to synthesize mitochondrial proteins, and to maintain them as fit organelles. In addition, we aim at searching for efficacious therapies in the mitochondrial disease COXPD1.

Specific aims. Based on the above we plan the following specific objectives:

Specific aim 1. Search for therapies in neurodegenerative diseases. Here we plan to perform a number of screening expeditions with the aim of identifying compounds that ameliorate the damage associated with GFM1 gene mutations in human cells. To this end, we will screen 50,300 compounds in human fibroblasts or in bacteria carrying mutant EFG1 proteins. In separate studies, we will analyze the therapeutic capacity of specific compounds that have been identified as potential mitochondrial boosters by the members of the proposal. Selected compounds with beneficial properties in human fibroblasts will be subjected to preclinical studies in mice, and if successful we would design a clinical proof of concept.

Specific aim 2. Search of processes downstream of EFG1. We plan to identify compensatory mechanisms operating in human cells expressing a mutant GFM1 protein. In this connection, we aim to characterize in depth translation of mitochondrial proteins by performing global ribosome profiling and mitoribosome profiling in control and GFM1 mutant fibroblasts in parallel to RNA-Seq analysis. Based on those observations, we will also explore the interaction of outer mitochondrial membrane proteins with RNA-binding proteins in control and diseased fibroblasts. In all, these data will permit us to identify potential mechanisms that compensate for the deficient mitochondrial protein synthesis.

We want to emphasize that this proposal is not a continuation of what is being done either at the HSJD or at IRB Barcelona. Instead, the proposal has been designed on the basis of the clinical and molecular expertise by the two investigators. We also want to mention that this will be the first step to look for other mechanisms in neurodegeneration in metabolic disorders that will led to a prospective source of therapies and potential new biomarkers.

Scientific plan.

Workplan related to Specific aim 1. Search for therapies in neurodegenerative diseases.

This workplan aims to identify compounds which show beneficial properties in human fibroblasts carrying GFM1 mutations. In an initial phase we plan to perform different screening expeditions that permit to identify compounds with some beneficial activity. To this end, we will use fibroblasts from three COXPD1 patients that carry compound heterozygous mutations (p.Arg671Cys and p. Gly469Val fs*84; p.Arg671Cys and p.Thr60Ser; p.Arg671Cys and p.Thr60Ser) in EFG1 protein (obtained from Ramon Martí, Hospital Vall d'Hebron). These fibroblasts show a reduced EFG1 protein expression, altered mitochondrial translation, and reduced activity of respiratory complexes I and IV, which is parallel to depressed mitochondrial respiration (Javier Torres-Torronteras and Ramon Marti, unpublished observations).

1A. Screening of compounds. In an initial phase, we will screen for compounds with the capacity to ameliorate some of the properties of the mutant fibroblasts. We plan to perform the following studies:

a. Screening in human fibroblasts carrying mutant GFM1 incubated in a galactose medium with a library of 50,300 compounds (IRB library). We will identify compounds that prevent cell death induced upon incubation of GFM1 mutant fibroblasts in the presence of galactose as an energy substrate instead of glucose [28]. In preliminary studies, we will analyze which fibroblasts show the optimal response to galactose. The screening will be performed at the Drug Screening Platform at IRB Barcelona. The IRB library is composed of 48,000 ChemDiv. compounds selected by chemical diversity and 2,300 FDA approved drugs.

b. Screening in bacteria expressing wild-type or mutant GFM1 (replacing the bacterial gene) with the IRB library. Here, we plan to generate bacteria strains expressing either the mutant version of EFG1 (p.Arg671Cys) or the wild-type protein, and we will search for the compounds that rescue growth. This will be followed by molecular modelling, and re-screening in fibroblasts carrying GFM1 mutations. These studies will be performed in collaboration with by Dr. Lluís Ribas de Pouplana, an expert in protein synthesis (IRB Barcelona). Briefly, this approach is based on the well-stablished strategy for the generation of bacterial tester strains, where an essential *E. coli* gene is substituted by the gene of interest (in this case, we would substitute *E. coli* EF-G by human EFG1). Once this modified strain is obtained it can be used to characterize mutations or quickly search for small molecules capable of modulating the activity of EFG1. An added complexity on the case of *E. coli* EF-G stems from the fact that this bacterial enzyme is involved in two different translation steps: elongation and ribosomal recycling. Since human EFG1 is only involved in elongation it is not possible to directly substitute *E. coli* EF-G with human EFG1. Fortunately, some bacterial species have duplicated EF-G and segregated the two functions of the enzyme in two independent proteins [29]. Thus, our strategy will be to first construct an *E. coli* strain that expresses a second EF-G from a different bacterial species that will complement the function of the *E. coli* enzyme in ribosome recycling. Once this first strain is obtained we will replace *E. coli* EF-G with human EFG1 to complement the elongation function of the *E. coli* enzyme.

c. Screening and development of a selected number of mitochondrial boosters already developed at IRB Barcelona by the members of the proposal, in fibroblasts from control subjects or in fibroblasts carrying GFM1 mutations. We have identified three structurally-related compounds that restore mitochondrial morphology and respiration under conditions of mitochondrial dysfunction induced genetically or pharmacologically, both in mice and human cell lines. Structurally related compounds are also being analyzed at present. These compounds show potencies in the low nanomolar range, high permeability and hepatic metabolism compatible with one or two daily doses. Based on these observations, we plan to analyze whether these compounds have the capacity to rescue some of the metabolic alterations of fibroblasts carrying GFM1 mutations.

d. Validation of the candidate compounds. In a further step, we will validate the compounds identified in the screening steps a and b, and we will analyze its potency in assays performed in human fibroblasts. Although, we foresee to identify several potential compounds, we only plan to move forward those with the lowest EC50 values (in the nanomolar or in the low micromolar range).

1B. Preclinical studies with selected compounds. The section will be composed of many potential steps but we just want to specify the intial ones.

a. Delineation of the effects of the initial hits in human fibroblasts carrying GFM1 mutations. Based on the screening expeditions generated in the prior section, we will select a number of initial hits that will be subjected to further analysis of their biological effects in human fibroblasts (control or carrying GFM1 mutations). The effects of the hit compounds (different concentrations, and time exposure) on EFG1 protein expression, the extent of mitochondrial stress response, mitochondrial translation, and mitochondrial respiration will be analyzed. Our expectations are to select a maximum of two compounds (named here as advanced hit compounds) with sufficient efficacy to permit further in vivo studies.

b. Proof of concept of two advanced hit compounds in a mouse model of hepatoencephalopathy. Ramon Marti and colleagues have recently documented a mouse model of COXPD1 [20]. Compound heterozygous $Gfm1^{R617C/-}$ mice show impaired mitochondrial translation, and a deficient mitochondrial respiration activity, making it a suitable mouse model for the study of COXPD1. Based on these findings, we plan to treat these mice with the selected compounds (at two doses for 30 days in initial studies). Depending on the existing knowledge on the compounds selected, and prior to the in vivo studies we will have to explore the maximal tolerated dose in mice, and also to perform in vivo pharmacokinetics. This latter will be done by contract through a CRO company as we have done it in similar studies. In chronic mouse studies, the following assays will be performed: a) expression of EFG1 protein in different tissues; b) histology in tissues (H&E, Oir Red O); c) plasma biochemistry; d) mitochondrial respiration in liver and brain. Depending on the data, we will analyze the activation of mitochondrial stress response pathways.

If some of these studies were successful, we would apply for additional funds that permit the acceleration of Innovation projects such as Caixa Research Validate (Fundació La Caixa), Proof of Concept (Ministerio de Ciencia e Innovacion), Valorization and Transfer of Research Results (AGAUR, Generalitat de Catalunya), or others available in due time. In all, we foresee generating a preclinical package with the most advanced compound.

1C. Design of a clinical trial. Based on the results of the preclinical studies with the selected compounds, an interventional study (clinical trial) will be developed. The primary objective of the study will be to evaluate the efficacy and safety of the proposed compound. To this end, the clinical trial will be designed tailored for the specific compound, considering its potential pharmacological effects. The dose of the compound will be calculated in relation to age and weight of the participant. The inclusion and exclusion criteria will be defined in relation to the specific compound. The potential participants will be clinically assesed sistematically. A baseline clinical assessment will be performed considering the age and neurodevelopmental status. A neurological examination will be performed, together with neurodevelopmental scales (Gross Motor Function Classification System, Vineland Adaptive Behavior Scales), as well as quality of life questionnaires (NeuroQoL) completed by the caregiver. The clinical assessment will be repeated 2 months after the baseline evaluation, and then 6 and 12 months after the first evaluation.

Other studies to be included are: ophtalmological assessment, cardiological assessment, abdominal ultrasound (hepatomegaly), biochemical biomarkers (acid-base balance, serum lactate, serum liver profile), cerebral MRI, and a safety follow-up.
The primary outcome measure, considering the specific condition, will be the change from baseline in a (1) neurodevelopmental scale/assesment and/or (2) the change in quality of life questionnaires at month 12. Secondary outcome measures will be considered (ie. change from baseline: biochemical/metabolic serum profile).

Workplan related to Specific aim 2. Search of processes downstream of EFG1.

We plan to identify compensatory mechanisms operating in human cells expressing a mutant EFG1 protein. Because the primary alteration induced by the mutations of EFG1 protein is an alteration of protein synthesis, we will characterize in depth the translation of mitochondrial proteins by performing global ribosome profiling and mitoribosome profiling in control and GFM1 mutant fibroblasts in parallel to RNA-Seq analysis. We will also explore the translational processes operating at the outer mitochondrial membrane proteins with RNA-binding proteins in control and diseased fibroblasts.

2A. Analysis of mitochondrial translation by ribosome profiling in control or GFM1 mutant fibroblasts.

In order to analyze the specific alteration occurring in mitochondrial translation or in translation in cells harboring mutations in GFM1, we will use ribosome profiling or mitoribosome profiling, deep sequencing-

based technologies that allow quantitative analysis of translation at nucleotide resolution [30-32]. Ribosome profiling maps the positions of ribosomes on transcripts by nuclease footprinting, generating nuclease-protected mRNA fragments bound to ribosomes that are converted into a DNA library suitable for deep sequencing[30, 31]. Mitochondrial ribosome profiling of human cells is based on digesting unprotected mRNA with micrococcal nuclease and mitoribosomes are separated from cytosolic ribosomes and other RNAs by ultracentrifugation in a single straightforward step [32, 33]. These studies will be in close collaboration with Raúl Méndez, an expert in the field. In parallel to these studies, we will perform transcriptomics by RNA-Seq in control and GFM1 mutants fibroblasts. In all, our data will identify translational processes that are modulated in human cells upon deficiency of a mitochondrial translation factor, and we hope that some of them are amenable for pharmacological manipulation.

2B. Identification of RNA-binding proteins present at the vicinity of mitochondria and that participate in mitochondrial biogenesis in control and GFM1 mutant fibroblasts.

In connection with mitochondrial protein biosynthesis, the vast majority of mitochondrial proteins are translated in the cytosol and imported into the mitochondria. Current models, derived from work in yeast and mammalian cells, suggest that the translation of many of the mitochondrial proteins occur in close vicinity to the mitochondrial outer membrane by localized ribosomes [34-39] ENREF_34 ENREF_34. Analysis of RNA-sequencing using proximity labeling of RNAs has revealed that there are many mRNAs localized at the outer mitochondrial membrane in mammalian cells [36]. Part of the RNAs are localized to mitochondria in a microtubule-dependent manner, some are translation-dependent, and others are recruited independently of their translation, via their 3′-UTRs [36]. Interestingly, this latter class of mRNAs was enriched with those encoding mitochondrial ribosome and OXPHOS components that require coordinated import and assembly, and likely depend on RNA-binding proteins (RBPs) [36]. mRNA recruitment near the mitochondria is not necessarily directly linked to translation since ribosome profiling experiments in yeast did not find the same RNAs that were localized to mitochondria using microarrays and fluorescent in situ hybridization [35, 40, 41].

In this section we aim to study whether fibroblasts carrying GFM1 mutation show an altered repertoire of mRNA and RNA-binding proteins in the vicinity of mitochondria, and whether this could be exploited as a strategy to fight against those alterations. This is particularly interesting provided that there is a profund implication of RNA-binding protein in neurodegenerative diseases [42, 43]. Some of the members of the proposal have identified a substantial number of RNA-binding proteins (around 30 candidates) as partners of mitochondrial fusion proteins localized at the outer mitochondrial membrane in human cells. We plan to validate whether some of those candidates are functionally relevant and whether undergo rearrangement upon EFG1 mutations. These studies will be performed in close collaboration with Raúl Méndez at the IRB.

Outcomes.

The major outcomes we foresee are the following:

- The activities performed in this proposal will permit to bring clinical activity closer to IRB Barcelona. This will be done since the start of the project by propitiating meetings between the members of the consortium, members of the Hospital San Joan de Déu and members of the IRB Barcelona.

- We plan to generate a number of candidates as potential mitochondrial boosters. This will be PI protected, and analyzed for other neurodegenerative or mitochondrial diseases.

- A carefully selected compound will develop into preclinical phase, and a clinical assay will be designed. If that is the case, an efficient pathway to channel this knowledge would be the generation of a biotech company.

- This multidisciplinary approach proposes a transformative research that will change our understanding on the mechanisms that drive neurodegeneration. The starting point will be COXPD1 disease, and it may expand into others based on the clinical knowledge present in house.

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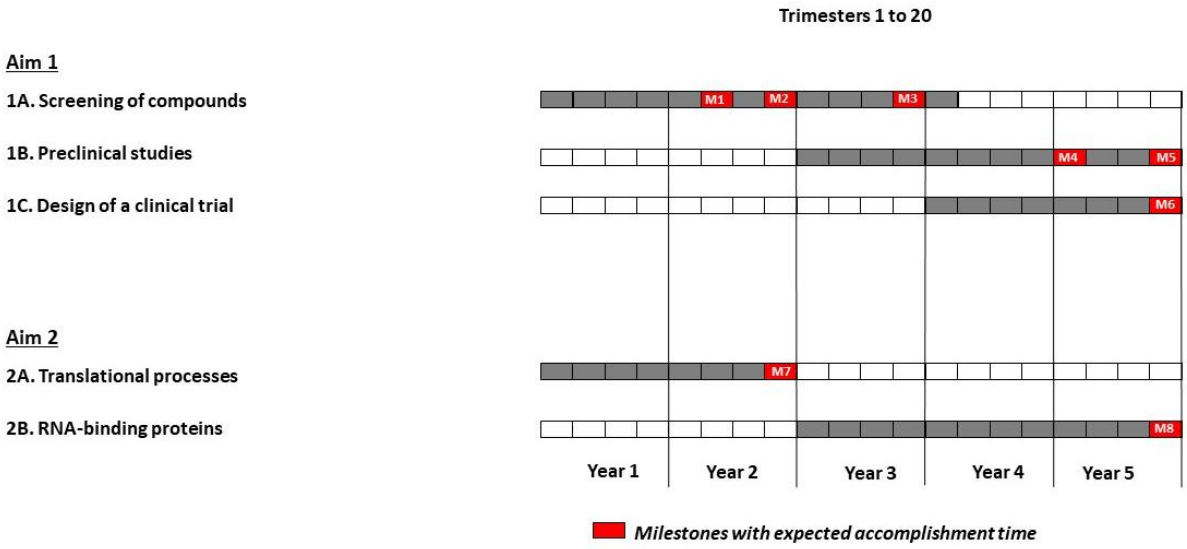
4. *PROJECT MILESTONES* / *Up to 1 page*

Provide an outline of major milestones and deliverables for the study.

We expect having 6 researchers working in the MENCIA LAB, which includes the Co-PIs Alejandra Darling and Antonio Zorzano. The New Group will interact with the collaborators mentioned in section 7, and they will synergize in the different activities. Alejandra Darling will be at the laboratory a minimum of one day a week. We also expect that the new group will grow based on grants obtained through public calls or by private donations.

The milestones of the project are shown in the scheme



M1- Identification of hit compounds obtained by screening of diseased fibroblasts.
M2- Identification of hit compounds in bacteria showing beneficial effects in the presence of mutant EFG1.
M3- Validation of candidate compounds.
M4- Characterization of the effects of advanced hit compounds in diseased fibroblasts.
M5- Proof of concept of advanced hit compounds in a mouse model of COXPD1.
M6- Design of a clinical trial.
M7- Ribosome and mitoribosome profiling in diseased fibroblasts.
M8- RNA-binding proteins in the vicinity of mitochondria from diseased fibroblasts.

Deliverables. Major deliverables will be:
D1- Obtaining funding from public-private foundations.
D2- Tightening the collaboration between IRB and HSJD.
D3- Joint supervision of two PhD students.
D4- An article on new compounds for the treatment of GFM1 mutations.

5. *SYNERGISTIC POTENTIAL OF THE PROJECT* / *Up to 2 pages*

Indicate the differences between the joint group proposal and a joint research project between two independent laboratories/institutions.

Provide a short description of the scientific and clinical questions that would have not been possible to tackle without TRIP-Clinics.

Indicate previous collaborations between the applicants (if any).

Briefly describe how will the participation of the clinical team contribute to strengthen the IRB Barcelona biomedical activities (beyond the joint group).

Outline the joint group growing plan, as well as the possible additional funding options to support it.

This proposal presents a series of well-defined strategic objectives, which are as follows. On the one hand, we aim to potentiate a Young Investigator as a future clinical and scientific leader in the country, in this case Alejandra Darling, a current staff member at the HSJD. To this end, she will have access to the technological capacities present at IRB Barcelona, and at HSJD, as well as Antonio Zorzano's experience. On the other hand, we intend to bring the clinical research of the HSJD closer to the research activity of IRB Barcelona through the generation of a mixed research group, and the activation of a set of measures that enhances interaction between members of the HSJD and IRB Barcelona.

This declaration of intent responds to one of the key questions in the generation of the TRIP-Clinics team proposed here. This will not be a usual collaboration between 2 research teams, but rather a new team will be created that is intended to have a high profile in the field, and become an international leader in the field of clinical neuropaediatrics.
Specifically, and from a scientific point of view, we aim to generate a new research group that combines the expertise at the IRB Barcelona and clinical research capacity of HSJD in order to fill the gap that exists between fundamental research and the design and generation of novel treatments in metabolic and neurodegenerative diseases. Beginning with a novel treatment in a specific case of a neurodegenerative disease (and also a mitochondrial disease), will be the first step that will lead us to that goal.

It should be noted that it is the continued interaction between the clinical and basic experience of the Co-IPs of the proposal that will allow the success of the proposed objectives. In this sense, the scientific objectives that we wish to obtain, for which the implementation of the MENCIA laboratory is absolutely necessary, are the following:
- Identification of hit compounds that have potential beneficial effects in the treatment of COXPD1 patients, their preclinical development, and the design of the clinical phase.
- Analysis of the translational mechanisms activated in COXPD1 patient cells, and possible use in therapy.
- Treatment of other pediatric neurodegenerative diseases through the processes or compounds described above. We also envision to obtain biomarkers (clinical, neuroimaging and biochemical), that in turn allow a standardized monitoring of potential new treatments.

Antonio Zorzano, through IRB Barcelona, has collaborated with different members of the HSJD for more than 15 years, which has given rise to 5 publications, the last one published in Aging Cell this year. Therefore, there is a remarkable mutual knowledge, and especially with Dr. Rafael Artuch, Chairman of the Department of Inborn Errors of Metabolism of the Clinical Biochemistry Laboratory, at HSJD, Luis Lores Coordinator of

Research at the Hospital General del Parc Sanitari Sant Joan de Déu. However, there has been no previous collaboration between the two co-PIs of this proposal.

As mentioned above, the generation of this TRIP-Clinics physically located in the IRB Barcelona facilities will contribute to strengthening the biomedical activities of the aforementioned institution beyond the implementation of the new group itself. In fact, the extensively defined team will be made up of 3 group leaders who work in two of the IRB Barcelona programs, plus an IRB Barcelona Platform Manager, and the future incorporation of another Computational Biology group is expected. By this, we mean that this proposal will involve the direct interaction of a large number of IRB Barcelona researchers with HSJD clinical researchers. On the other hand, the implementation of a set of initiatives associated with the operation of the laboratory is proposed:
- Invitation at the IRB Barcelona Biomed Seminar to clinical researchers in the field of pediatric neurodegeneration, attracting not only basic researchers but also clinical researchers from reference hospitals in Barcelona.
- Organization of IRB Barcelona Biomed Conferences where the program is both clinical and basic in the field of pediatric neurodegeneration.
- Organization of series of seminars in the field of pediatric neurodegeneration with the participation of both relevant members of operational clinical research in and around Barcelona and members of IRB Barcelona.
We believe that these additional activities will be a stimulus to increase the biomedical activities of IRB Barcelona.

The activities posed in this proposal clearly exceed the budget assigned according to the call. This is done on purpose just to make clear our intention to obtain resources beyond those obtainable directly through the TRIP call. In relation to this aspect, this proposal is supported by different Patient Associations and/or Foundations such as the "Association of Patients with Mitochondrial Pathologies" and the "Mencia Foundation". In this sense, we intend that the TRIP call be the seed that grows additionally through national or international competitive funds, and also through Innovation calls mentioned above, and those from Private Foundations. At this time, we are in contact with the ACS Foundation, and with the Mapfre Foundation. In any case, we will start the activity of the laboratory with two postdoctoral researchers in addition to the activity of the co-Pis. Next, we plan to incorporate two doctoral students from the IRB Barcelona and HSJD calls, and in a more advanced phase we plan to incorporate other researchers/technicians thanks to the aforementioned externally obtained funds.

6. *CV PRINCIPAL INVESTIGATORS* / *Free Format, up to 5 pages.*

Provide the CVs of the Project Leaders at IRB Barcelona and the Clinical Research Institution. There is no established format but limited to 5 pages.

CV Date	03/07/2022

Part A. PERSONAL INFORMATION

First Name *	Alejandra		
Family Name *	Darling		
Sex *	Female	Date of Birth *	16/11/1976
ID number Social Security, Passport *	30361592M	Phone Number *	(0034) 934330186
URL Web			
Email Address	alejandra.darling@sjd.es		
Researcher's identification number	Open Researcher and Contributor ID (ORCID) *	0000-0003-0344-5809	
	Researcher ID		
	Scopus Author ID		

* Mandatory

A.1. Current position

Job Title	Facultativo Especialista		
Starting date	2015		
Institution	Hospital Sant Joan de Déu		
Department / Centre			
Country		Phone Number	
Keywords			

A.2. Previous positions

Period	Job Title / Name of Employer / Country
2012 - 2014	Medical Assistant / Hospital Mataro
2008 - 2012	Fellowship / FLENI (Fundación para la Lucha de Enfermedades Neurológicas de la Infancia)

A.3. Education

Degree/Master/PhD	University / Country	Year
Especialista en Pediatría y Áreas específicas Homologado en España	Ministerio de Sanidad de España	2021
Doctorado en Medicina	Universidad de Barcelona - Facultad de Medicina	2019
Máster en Neurología Infantil	Hospital Materno Infantil "Sant Joan de Déu". Universidad de Barcelona	2014
Especialista en Neurología Infantil	Ministerio de Salud y Ambiente de la República Argentina	2014
Médico homologado al título universitario oficial español	Ministerio de Educación de España	2011
Médico Universitario Especialista en Pediatría	Universidad de Buenos Aires (UBA), Argentina	2007
Médico Especialista en Pediatría	Ministerio de Salud y Ambiente de la República Argentina	2007
Licenciado en Medicina	Universidad de Buenos Aires, Argentina	2003

A.4. General quality indicators of scientific production
Clinical Trials - Participation:

1- A Study to Assess the Efficacy and Safety of Vatiquinone for the Treatment of Participants With Friedreich Ataxia (MOVE-FA). Sponsor: PTC Therapeutics. Ongoing. Role: Principal Investigator.
2- A Clinical Study to Evaluate the Effect of MIN-102 on the Progression of Friedreich's Ataxia in Male and Female Patients (FRAMES). Sponsor: Minoryx Therapeutics, S.L. Finalization: 2020. Role: Principal Investigator.
3- A Randomized, Double-blind, Placebo-controlled, Multinational, Multicenter Study With Open-label Treatment Extension to Assess the Effect of MIN-102 (IMP) on the Progression of Adrenomyeloneuropathy in Male Patients With X-linked Adrenoleukodystrophy. Sponsor: Minoryx Therapeutics, S.L. Ongoing. Role: Sub-Investigator.
4- A multicenter, multinational, randomized, doublé-blind, placebo controlled study to assess the efficacy, pharmacodynamics, pharmacokinetics, safety, and tolerability of venglustat in late-onset GM2 gangliosidosis and ultra-rare diseases within the same and similar glucosylceramide based sphingolipid pathway. Sponsor: Genzyme Corporation. Ongoing. Role: Sub-Investigator.

Participation – Membership -European Reference Networks (ERN):
- ERN for Rare Neurological Diseases (ERN-RND):
1- Dystonia & NBIA disorders
2- Ataxias & paraparesis.
- ERN for Hereditary Metabolic Disorders (MetabERN)

Prizes:
- Best Poster presentation Prize for the contribution "Expanding the neurological spectrum of seipin deficiency (BSCL2): a complex lipid defect". 13th European Paediatric Neurology Society Congress (EPNS). Athens, Septiembre 2019.
- Best Oral presentation Prize "Panthothenate Kinese Associated Neurodegeneration: Clinical Assessment and genetic characterization by means of a Spanish Multicenter Research Network" 11th European Paediatric Neurology Society Congress (EPNS) 2015
- Beca Premio SENEP por el trabajo "Enfermedades Nerodegenerativas por acumulación cerebral de hierro: estudio multicéntrico colaborativo" SENEP 2014
- Beca Premio SENEP "Nerodegeneración con acúmulo de hierro cerebral: heterogeneidad clínica y genética" Congreso Nacional de la Sociedad española de Neurología Pediátrica. SENEP 2013

Part B. CV SUMMARY
I have the medical degree obtained in the University of Buenos Aires, in Argentina. As a student I followed teaching activities in histology and embryology. Once I finished my studies in Pediatrics, and since my initial training in Neuropediatrics, I have been interested in the area of complex motor disorders, including patients with rare diseases, neurometabolic conditions.
During the studies in the Master in Neurology in the Barcelona University, at the Sant Joan de Déu hospital, together with Dr. Ángels García-Cazorla, coordinator of the Metabolic Diseases Unit, I had the opportunity to assess patients with early onset movement disorders, including ataxia, dystonia, complex paraparesis and parkinsonism.
After this period, I have collaborated in the development of a project aimed at studying a group of rare diseases known together as, Neurodegeneration with Brain Iron Accumulation (NBIA) disorders. The study of this group of diseases, as well as the design of an instrument designed to clinically assess severity, has been the focus of study in my doctoral thesis that led to obtain the title of Doctor in Medicine.

Currently, I´m a medical assistant in the Pediatric Neurology Service of the Sant Joan de Déu Hospital, I work in the Unit of Metabolic Diseases and the Movement Disorders Unit. This setting allows me to have a broad vision in patients with complex motor disorders and integrate care and research.

Part C. RELEVANT ACCOMPLISHMENTS

C.1. Publications

AC: corresponding author. (nº x / nº y): position / total authors. If applicable, indicate the number of citations

1 **Scientific paper**. 2022. Assessing the landscape of STXBP1-related disorders in 534 individuals Brain.
2 **Scientific paper**. 2021. Plasma idebenone monitoring in Friedreich's ataxia patients during a long-term follow-up Biomedicine and Pharmacotherapy.
3 **Scientific paper**. Marta Montpeyó; Marta Correa Vela; Vincenzo Lupo. 2020. Impaired proteasome activity and neurodegeneration with brain iron accumulation in FBXO7 defect Annals of Clinical and Translational Neurology. 7-8, pp.1436-1442. https://doi.org/10.1002/acn3.51095
4 **Scientific paper**. Fernandez Marmiesse; Sanchez Iglesias; Darling. 2019. A de novo heterozygous missense BSCL2 variant in 2 siblings with intractable developmental and epileptic encephalopathy.Seizure. https://doi.org/• 10.1016/j.seizure.2019.07.019
5 **Scientific paper**. Alejandra Darling. 2019. PLA2G6-associated neurodegeneration: New insights into brain abnormalities and disease progression Parkinsonism and Related Disorders. 61, pp.179-186. https://doi.org/• 10.1016/j.parkreldis.2018.10.013
6 **Scientific paper**. 2018. Frameless robot-assisted pallidal deep brain stimulation surgery in pediatric patients with movement disorders: precision and short-term clinical results J Neurosurg Pediatr. 20, pp.1-10. https://doi.org/10.3171/2018.5.PEDS1814
7 **Scientific paper**. 2018. Gamma-aminobutyric acid levels in cerebrospinal fluid in neuropaediatric disorders Dev Med Child Neurol. 60-8, pp.780-792. https://doi.org/10.1111/dmcn.13746
8 **Scientific paper**. 2018. Hypermanganesemia due to mutations in SLC39A14: further insights into Mn deposition in the central nervous system Orphanet J Rare Dis. 13-1, pp.28. https://doi.org/• 10.1186/s13023-018-0758-x
9 **Scientific paper**. 2017. Clinical rating scale for pantothenate kinase-associated neurodegeneration: A pilot study.Movement Disorders. Wiley Online Library. 32-11, pp.1620-1630. https://doi.org/10.1002/mds.27129
10 **Scientific paper**. Tello, C; Darling, A. 2017. On the complexity of clinical and molecular bases of neurodegeneration with brain iron accumulation Clinical Genetics. Wiley Online Library. 2017, pp.1-10. https://doi.org/10.1111/cge.13057
11 **Scientific paper**. 2017. Thiamine deficiency in childhood with attention to genetic causes: Survival and outcome predictors Annals of Neurology. Wiley Online Library. 82-3, pp.317-330. https://doi.org/10.1002/ana.24998
12 **Scientific paper**. 2017. Twin-sisters with PLA2G6-associated neurodegeneration due to paternal isodisomy of the chromosome 22 following in vitro fertilization Clinical Genetics. Wiley Online Library. 92-1, pp.117-118. https://doi.org/10.1111/cge.12925
13 **Scientific paper**. 2013. Medication-related oculogyric crises: a description of four cases and a review of the literature Revista de Neurología. Viguera. 56-3, pp.152-156.

C.2. Conferences and meetings

1 Altered autophagy mechanisms associated with neurodegeneration: Study of a cohort of patients with Beta-Propeller protein-Associated Neurodegeneration (BPAN). EPNS Congress (European Pediatric Neurology Society) 2022. EPNS. 2022.
2 Early-onset ataxia associated with ITPR1 mutations: Pediatric cohort, clinical, radiological, and genetic characterization. EPNS (European Pediatric Neurology Society) Research Meeting 2022. EPNS. 2022.

3 Patterns of abnormal movements in inherited metabolic disorders with neonatal presentation. EPNS Congress (European Pediatric Neurology Society) 2022. EPNS. 2022.

C.3. Research projects and contracts

1 **Project**. Developing patient-tailored therapeutic candidates for rare genetic forms of Pediatric Parkinsonism. (Hospital Sant Joan de Déu). From 2020.
2 **Project**. Neurodegeneration with Brain Iron Accumulation: Clinical Assessment and genetic Characterization by means of a Spanish multicenter research network. Marató TV3. Belén Pérez Dueñas. (Fundació Hospital Sant Joan de Déu). From 2015.
3 **Healthcare project**. "Neurodegeneration with Brain Iron Accumulation: Clinical Assessment and genetic Characterization by means of a spanish multicenter research network". (Fundació Hospital Sant Joan de Déu). From 2015. €.

CV date	10/5/2022

Part A. PERSONAL INFORMATION

First and Family name	Antonio Zorzano Olarte		
Social Security, Passport, ID number	46025113C	Age	65
Researcher numbers	Researcher ID		
	Orcid code	0000-0002-1638-0306	

A.1. Current position

Name of University/Institution	• Full Professor of Biochemistry and Molecular Biology. Universitat de Barcelona. • Group leader at IRB Barcelona. • Programme Coordinator and Group leader at CIBERDEM		
Department	• Facultad de Biología, Departamento de Bioquimica y Biomedicina Molecular; • Aging and Metabolism Programme, IRB Barcelona; • Programme of Mechanisms of Diabetes Development, CIBERDEM.		
Address and Country	Baldiri Reixac,10 (08028 Barcelona)		
Phone number	+34934037199	E-mail	antonio.zorzano@irbbarcelona.org
Current position	Full Professor of Biochemistry and Molecular Biology	From 1991	
Espec. cód. UNESCO	230215, 230217, 230219, 230221		
Key Words	Mitochondrial dynamics; autophagy; metabolic homeostasis; insulin resistance; liver damage; type 2 diabetes; obesity		

A.2. Education

PhD	University	Year
BSc and Master in Biology	University of Barcelona	1978
Ph.D. in Biology	University of Barcelona	1982

A.3. JCR articles, h Index, thesis supervised…

Since 2012 the Zorzano laboratory published 39 articles with Antonio Zorzano as senior author. My global numbers are: **H-index: 93 (Google Scholar)**; Total publications indexed in PubMed: 351; **Publications with 100 cites: 86 (Google Scholar)**; **Total number of cites: 39,111 (WoS)**; Number of 6-years Research periods positively evaluated: 7. Last 6-year period evaluated: 2015-20. Number of Ph.D. thesis supervised in the last 10 years: 17.
Publications last 5 years in first quartile (Q1): 70; This includes 26 articles with impact factor greater than 9 (1 Cell, 2 Cell Metab, 2 Nat. Cell Biol., 1 Nat. Immunol., 1 Circulation, 4 Nat. Commun., 1 Dev. Cell, 4 EMBO J., 1 Trends Mol.Med., 1 Trends Endocrinol. Metab., 1 Aging Res. Rev, 1 Clin. Cancer Res., 2 Autophagy, 4 PNAS, 2 Cell Reports.

Part B. CV SUMMARY *(max. 3500 characters, including spaces)*

Currently Professor of Biochemistry and Molecular Biology at the University of Barcelona, Group Leader at IRB Barcelona and Program coordinator at CIBERDEM. He completed his Ph.D. at the University of Barcelona, and postdocs with Dr. Emilio Herrera (Ramon y Cajal Hospital, Madrid), Neil Ruderman (Boston University Medical Center), and Paul Pilch (Boston University Medical School). He has supervised 39 doctoral theses and has coordinated and participated in international consortiums funded by different European institutions. Co-inventor of 22 patents and founder of biotechnological companies (Xcellsyz, Genmedica Therapeutics).

Zorzano discovered a specific mechanism of rapid modulation of GLUT4 glucose transporters in the adipocyte in response to insulin as well as a set of relevant mechanisms in the control of the activity of GLUT1 and GLUT4 transporters in mammalian cells, and their role in pathology. Recently, he has demonstrated the role of proteins of mitochondrial dynamics in the control of metabolism, and their role in conditions of insulin resistance as well as in liver damage. Finally, his laboratory has documented the role of the autophagic protein TP53INP2 in the control of adiposity and muscle mass in animal models.
His current research focuses on the regulation of metabolism and its interaction with insulin resistance, obesity, type 2 diabetes and its complications. His current interests link metabolism with mitochondrial dynamics, mitochondrial function, autophagy and mitochondrial stress. A global objective of their group is to identify and validate mitochondrial targets that allow the prevention or treatment of insulin resistance, type 2 diabetes or obesity through the use of cell-based systems, genetically modified mice, and clinical material obtained from patients.

Part C. RELEVANT MERITS (Last 10 years)
C.1. Publications (including books)

1. Irazoki A., Gordaliza-Alaguero I., Giakoumakis N.N., Palacín M., Gumà A., Sebastián D & **Zorzano A**. Disruption of mitocondrial dynamics triggers muscle inflammation through interorganellar contacts and mtDNA mislocation. Invited resubmission to Nat. Commun.

2. Naón D., Hernández-Alvarez M.I., Martins de Brito O., Quintana A., Hidalgo J., Palacín M., Aparicio P., Castellanos J., Lores L., Sebastián D., Fernández-Veledo S., Vendrell J., Joven J., **Zorzano A***., Scorrano L*. (* shared senior authorship). Alternatively spliced Mitofusin 2 variants control endoplasmic reticulum tethering to mitochondria and liver homeostasis. Invited resubmission to Science.

3. Sabaté-Pérez A., Romero M., Carobbio S., Mouratidis M., Sala D., Engel P., Villena J.A., Virtue S., Vidal-Puig A., Palacín M., Testar X., **Zorzano A**. Autophagy-mediated NCoR1 degradation is required for brown fat maturation and thermogenesis. Invited resubmission to Autophagy.

4. Irazoki A, Martinez-Vicente M, Aparicio P, Aris C, Alibakhshi E, Rubio-Valera M, Castellanos J, Lores L, Palacín M, Gumà A, **Zorzano A***, Sebastián D*. (* shared senior authorship). Coordination of mitochondrial and lysosomal homeostasis mitigates inflammation and muscle atrophy during aging. Aging Cell. 2022 Mar 9:e13583. doi: 10.1111/acel.13583.

5. Sun-Wang JL, Yarritu-Gallego A, Ivanova S, **Zorzano A**. The ubiquitin-proteasome system and autophagy: self-digestion for metabolic health. Trends Endocrinol Metab. 2021 Aug;32(8):594-608. doi: 10.1016/j.tem.2021.04.015. Epub 2021 May 22.

6. Sebastián D, **Zorzano A**. Self-Eating for Muscle Fitness: Autophagy in the Control of Energy Metabolism. Dev Cell. 54, 268-281, 2020.

7. Tur J, Pereira-Lopes S, Vico T, Marín EA, Muñoz JP, Hernández-Alvarez M, Cardona PJ, **Zorzano A**, Lloberas J, Celada A. Mitofusin 2 in Macrophages Links Mitochondrial ROS Production, Cytokine Release, Phagocytosis, Autophagy, and Bactericidal Activity.
Cell Rep. 2020;32(8):108079. doi: 10.1016/j.celrep.2020.108079.

8. Sun-Wang JL, Ivanova S, **Zorzano A**. The dialogue between the ubiquitin-proteasome system and autophagy: implications in ageing. Ageing Res Rev. 2020. doi: 10.1016/j.arr.2020.101203. Online ahead of print.

9. Gordaliza-Alaguero I, Cantó C, **Zorzano A.** Metabolic implications of organelle-mitochondria communication. EMBO Rep. 20, e47928, 2019.

10. Hernández-Alvarez MI, Sebastián D, Vives, Ivanova S, Bartoccioni P, Kakimoto P, Plana N, Veiga SR, Hernández V, Vasconcelos N, Peddinti G, Adrover A, Jové M, Pamplona R, Gordaliza-Alaguero I, Calvo E, Cabré N, Castro R, Kuzmanic A, Boutant M, Sala D, Hyotylainen T, Orešič M, Fort J, Errasti-Murugarren E, Orozco M, Joven J, Cantó C, Palacin M, Fernández-Veledo S, Vendrell J, **Zorzano A**. Deficient ER-mitochondrial phosphatidylserine transfer causes liver disease. Cell 177, 881-895, 2019.

11. Ivanova S, Polajnar M, Hernandez Alvarez MI, Slobodnyuk K, Plana N, Nebreda AR, Palacin M, Gomis R, Behrends C., **Zorzano A**. Autophagic protein TP53INP2 regulates death receptor-induced apoptosis by scaffolding TRAF6 and caspase-8. EMBO J. 38, pii: e99300, 2019.

12. Romero M, Sabaté-Pérez A, Francis VA, Castrillón-Rodriguez I, Díaz-Ramos A, Sánchez-Feutrie M, …., Gustafson B, Hammarstedt A, Fernández-Real JM, Vendrell J, Smith U, **Zorzano A**. TP53INP2 regulates adiposity by activating β-catenin through autophagy-dependent sequestration of GSK3β. Nat. Cell Biol. 20, 443-454, 2018.

13. Rodríguez-Nuevo A, Díaz-Ramos A, Noguera E, Díaz-Sáez F, Duran X, Muñoz JP, Romero M, Plana N, Sebastián D, Tezze C, Romanello V, Ribas F, Seco J, Planet E, Doctrow SR, González J, Borràs M, Liesa M, Palacín M, Vendrell J, Villarroya F, Sandri M, Shirihai O, **Zorzano A**. Mitochondrial DNA and TLR9 drive muscle inflammation upon Opa1 deficiency. EMBO J. 37, e96553, 2018.

14. Ramírez S, Gómez-Valadés AG, Schneeberger M, Varela L, Haddad-Tóvolli R, Altirriba J, Noguera E, Drougard A, Flores-Martínez Á, Imbernón M, Chivite I, Pozo M, Vidal-Itriago A, Garcia A, Cervantes S, Gasa R, Nogueiras R, Gama-Pérez P, Garcia-Roves PM, Cano DA, Knauf C, Servitja JM, Horvath TL, Gomis R, **Zorzano A***, Claret M*. (Co-corresponding authors). Mitochondrial Dynamics Mediated by Mitofusin 1 Is Required for POMC Neuron Glucose-Sensing and Insulin Release Control. Cell Metab. 25, 1390-1399, 2017.

15. Sebastián D, Sorianello E, Segalés J, Irazoki A, Ruiz-Bonilla V, Sala D, Planet E, Berenguer-Llergo A, Muñoz JP, Sánchez-Feutrie M, Plana N, Hernández-Álvarez MI, Serrano AL, Palacín M, **Zorzano A**. Mfn2 deficiency links age-related sarcopenia and impaired autophagy to activation of an adaptive mitophagy pathway. EMBO J. 35, 1677-93, 2016.

16. Zamudio-Vázquez R, Ivanova S, Moreno M, Hernandez-Alvarez MI, Giralt E, Bidon-Chanal **A, Zorzano A***, Albericio F*, Tulla-Puche J* (Co-corresponding authors). A new quinoxaline-containing peptide induces apoptosis in cancer cells by autophagy modulation. Chem. Sci., 6, 4537-4549, 2015.

17.Sala D, Ivanova S, Plana N, Ribas V, Duran J, Bach D, Turkseven S, Laville M, Vidal H, Karczewska-Kupczewska M, Kowalska I, Straczkowski M, Testar X, Palacín M, Sandri M, Serrano AL, **Zorzano A**. Autophagy-regulating TP53INP2 mediates muscle wasting and is repressed in diabetes. J. Clin. Invest. 124, 1914-1927, 2014.

18.Muñoz JP, Ivanova S, Sánchez-Wandelmer J, Martínez-Cristóbal P, Noguera E, Sancho A, Díaz-Ramos A, Hernández-Alvarez MI, Sebastián D, Mauvezin C, Palacín M, **Zorzano A**. Mfn2 modulates the UPR and mitochondrial function via repression of PERK. EMBO J. 32, 2348-2361, 2013.

19.Sebastián D, Hernández-Alvarez MI, Segalés J, Sorianello E, Muñoz JP, Sala D, Waget A, Liesa M, Paz JC,. Gopalacharyulu P, Orešič M, Pich S, Burcelin R, Palacín M, **Zorzano A**. Mitofusin 2 (Mfn2) links

mitochondrial and endoplasmic reticulum function with insulin signaling and is essential for normal glucose homeostasis. Proc Natl Acad Sci U S A. 109, 5523-5528, 2012.

C.2. Research projects and grants (as PI) (ongoing)

1. Coordinator and PI of the project entitled "Phospholipid biosynthesis and transport between endoplasmic reticulum and mitochondria: understanding their essential role in liver disorders", Fundación La Caixa. 2021-24. Budget : 997,014€

2. PI of the project "Development of first-in-class drugs to treat NASH (Drug4NASH)", Ministerio de Ciencia e Innovación (Proyectos Pruebas de Concepto). 2021-23. Budget : 149,500€

3. ICREA Acadèmia. Generalitat de Catalunya. 2020-24. Budget : 200,000€

4. PI of the project entitled "Mitochondrial dynamics as a key process to prevent muscle inflammation and search of novel therapies in inflammatory myopathies". AFM-Telethon. 2020-22. Budget : 90,000€

5. PI of the project entitled "Role of proteins involved in mitochondrial fusion and autophagy in the control of metabolism and inflammation, and impact in pathology". Ministerio de Ciencia e Innovación (PID2019-106209RB-I00). 2020-22. Budget : 411,400€

6. PI of the project entitled "Producción industrial en células de omega-3 (DHA y EPA) para su uso en alimentación (RTC2019-007154-2). Ministerio de Ciencia e Innovación. 2020-23. Budget: 156,980€

7. PI of the project entitled "ACE-2-derived peptide super-binders with enhanced efficacy for inhibition of SARS-COV-2 infection" funded by FONDO SUPERA COVID-19.2020-22. Budget: 33,075 €

8. Member of the Research Network "Biología y Medicina Redox" (RED2018-102576-T). Ministerio de Ciencia, Innovación y Universidades. 2019-22. Budget: no

9. CIBERDEM (CIBER de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III). 2011-. Budget: no

C.3. Contracts

C.4. Patents (last 10 years)

1. Title: Anti-inflammatory and antioxidant conjugates useful for treating metabolic disorders.
Inventors: J.C. Castro, S. García-Vicente, L. Marti, E. Mayoux, A. Mian, M. Serrano, A. Zorzano
Reference: EP 2408443 A1; WO2010106082A1
Priority date; 16 Mar 2009; Publication date: 25 Jan 2012

2. Title: Combination therapies for treating metabolic disorders.
Inventors: S. García-Vicente, L. Marti, E. Mayoux, A. Mian, M. Serrano, A. Zorzano
Reference: EP 2408441 A1; WO2010106083A1
Priority date; 16 Mar 2009; Publication date: 25 Jan 2012

3. Title: Thiocarbonates as anti-Inflammatory and antioxidant compounds useful for treating metabolic disorders.
Inventors: J.C. Castro, L. Marti, A. Zorzano, S. García-Vicente, A. Mian, A. Zorzano
Reference: US2012/0149769 A1
Priority date; 16 Sept 2011; Publication date: 14 Jun 2012

4. Title: Pharmaceutical combinations including anti-inflammatory and antioxidant conjugates useful for treating metabolic disorders
Inventors: Julio Castro, Luc Marti, Antonio Zorzano, Silvia Garcia-Vicente, Alec Mian
Reference: WO 2013037985 A8
Publication date: Apr 11 2013

5. Title: New thiocarbonates as anti-inflammatory and antioxidant compounds useful for treating metabolic disorders
Inventors: Julio Castro, Silvia Garcia-Vicente, Luc Marti, Alec Mian, Antonio Zorzano
Reference: WO 2012080371 A1
Publication date: Jun 21 2012

6. Title: Methods and uses of mitofusins.
Inventors: C. Canto Alvarez, S. Kulkarni, A. Zorzano
Reference: 14192012.4-1408
Publication date: Jan 30 2015

7. Title: Methods for improving the cell therapy efficacy with mesenchymal stem cell populations.
Inventors: Sonia Fernandez Veledo, Carolina Serena, Joan Vendrell, Antonio Zorzano.
Reference: EP17382615.7.
Submission date: September 18, 2017.

C.5 Awards

- ICREA Acadèmia, Generalitat de Catalunya. 2014-19, and 2020-2024.
- Alberto Sols Senior Investigator Award for Basic Sciences. Spanish Society of Diabetes 2011.
- UB Award to Special Dedication to Research (2008-10).
- Generalitat de Catalunya Award to Special Dedication to Reseach (2000-07).
- Young Investigator Award of the Spanish Society of Diabetes (1992).
- Boehringer Award of the Spanish Biochemical Society (1991).

C.6 Invitation to Congresses or International Meetings: more than 40 since 2016

7. KEY PERSONNEL / Up to 1 page

Provide a tabular list of the key personnel (PIs, associated researchers, postdocs, etc.) on the proposed study, as well as their institutional affiliation.

The members of the proposal show complementary clinical and basic knowledge on neurodegenerative and mitochondrial diseases and mitochondrial biology. The new research team will be constituted by:

-Alejandra Darling (Clinical Attending of Pediatric Neurology, Metabolic Disease Unit and Movement Disorders Unit, Hospital Sant Joan de Déu, Barcelona). Special interest in neurodegenerative and metabolic conditions.

-Antonio Zorzano (Molecular Biology, IRB Barcelona).

-In an initial stage, the Research team will be also composed by two postdoctoral fellows to be contracted by TRIP, and we also aim to recruit one PhD student through the international IRB Barcelona call, and another PhD student through HSJD.

Other key collaborators of the proposal will be:

- Rafael Artuch (Clinical Biochemist, Chairman of the Department of Inborn Errors of Metabolism of the Clinical Biochemistry Laboratory, and Group leader of the Unit-703 from CIBERER at the Inborn Errors of Metabolism Unit, Hospital Sant Joan de Déu, Barcelona). Great expertise in the management of patients with mitochondrial disorders.

- Angels García-Cazorla (Pediatric Neurologist, and Coordinator of the Metabolic Disease Unit and Synaptic Metabolism Lab, Hospital Sant Joan de Déu, Barcelona). She has a great clinical expertise in the management of patients with mitochondrial disorders and neurological findings.

- Ramon Martí (Head of the Research Group on Neuromuscular and Mitochondrial Diseases, Vall d'Hebron Research Institute, Hospital Universitari Vall d'Hebron). He has expertise in mitochondrial disorders, with special focus on those involving mtDNA maintenance and mitochondrial translation, and also specifically in combined oxidative phosphorylation deficiency type 1.

- Raúl Méndez (IRB Barcelona). Expert in regulation of translation and RNA-binding proteins.

- Israel Ramos (IRB Barcelona). His expertise as the Head of the Drug Screening Platform will be key for the success of the proposal.

- Lluís Ribas de Pouplana (IRB Barcelona). Expertise in mitochondrial protein synthesis and tRNA homeostasis.

-In due time we will also establish collaborations with experts in Computational Biology, that will be relevant to the analysis of the mechanisms of action of the advanced hit compounds identified.

8. BUDGET AND JUSTIFICATION / Up to 2 pages

Successful proposals will receive seed funding amounting to €150,000 annually over 3 years to cover direct expenses, with the possibility to extend the support for another 2 years subject to positive evaluation of both the group and the TRIP Programme.

Eligible expenses include personnel, consumable material and the use of scientific services, among others.

The allocation of seed funding to compensate the clinical research centre/hospital for the time dedicated to the proposed study by the practising MD participating in this endeavour is an eligible cost and should be included in the budget not exceeding the €150,000 limit.

BUDGET (3 Years)

Provide a concise cost breakdown.

	Year 1	Year 2	Year 3	TOTAL BUDGET
PERSONNEL Post Doc 1	38.278,00	38.278,00	38.278,00	114.834,00
PERSONNEL Post Doc 2	38.278,00	38.278,00	38.278,00	114.834,00
COMPENSATION TO COLLABORATING RESEARCH	30.000,00	30.000,00	30.000,00	90.000,00
CONSUMABLES	22.444,00	20.444,00	14.444,00	57.332,00
INTERNAL FACILITIES AND SERVICES	21.000,00	21.000,00	21.000,00	63.000,00
TRAVEL	0,00	2.000,00	2.000,00	4.000,00
PUBLICATIONS	0,00	0,00	6.000,00	6.000,00
TOTAL YEAR	**150.000,00**	**150.000,00**	**150.000,00**	**450.000,00**