Hospital Universitario y Politécnico La Fe

PROGRAMA 1 RD16/0022/0001
Intervenciones durante la gestación, período neonatal y edad pediátrica para la prevención y el tratamiento de la patología inmediata y de sus posibles consecuencias en la edad adulta.

Máximo Vento

Coordinador Red SAMiD

RD16/0022/0001

Instituto de Investigación Sanitaria La Fe

REDES TEMÁTICAS DE INVESTIGACIÓN COOPERATIVA EN SALUD

DATOS DE LA SOLICITUD

Para que esta solicitud sea válida ES IMPRESCINDIBLE que tenga entrada entre el martes, 05 de abril de 2016 y el jueves, 05 de mayo de 2016 inclusive, con la firma original del representante legal del centro, en alguno de los Registros Públicos regulados en el artículo 38.4 de la Ley 30/1992, de 26 de noviembre, de Régimen Jurídico de las Administraciones Públicas y del Procedimiento Administrativo Común.
Para que la solicitud sea ADMITIDA No olvide enviar a la Subdirección General de Evaluación y Fomento de la Investigación, en el formato exigido, los documentos específicos que la convocatoria considera parte integrante de la solicitud

EXPEDIENTE: RD16/0022/0001 **INVESTIGADOR PRINCIPAL:** VENTO TORRES, MAXIMO

RED TEMÁTICA DE INVESTIGACIÓN COOPERATIVA EN SALUD

ÁREA TEMÁTICA:	Salud materno-infantil y del desarrollo
NOMBRE RED:	RED DE SALUD MATERNO-INFANTIL Y DEL DESARROLLO
COORDINADOR DE RED:	VENTO TORRES, MAXIMO

CENTRO SOLICITANTE

Código:	1645
Centro Solicitante	FUNDACION PARA LA INVESTIGACION DEL HOSPITAL LA FE

CENTRO REALIZACIÓN

Código	460018
Centro Realización	HOSPITAL LA FE

PRESUPUESTO POR ANUALIDADES Y PROGRAMA

PROGRAMA	AN.	FORMACIÓN Y COORDINACIÓN	VIAJES	BIENES/SRV	PERSONAL	OVERHEAD	TOTAL
Intervenciones durante la gestación, período neonatal y edad pediátrica para la prevención y el tratamiento de la patología inmediata y de sus posibles consecuencias en la edad adulta.	1	0,00	9.000,00	2.000,00	59.000,00	7.000,00	77.000,00
	2	0,00	9.000,00	2.000,00	59.000,00	7.000,00	77.000,00
	3	0,00	9.000,00	2.000,00	59.000,00	7.000,00	77.000,00
	4	0,00	9.000,00	2.000,00	59.000,00	7.000,00	77.000,00
	5	0,00	9.000,00	2.000,00	59.000,00	7.000,00	77.000,00
Cardiovascular risk related prenatal factors	1	0,00	2.000,00	2.000,00	29.500,00	3.350,00	36.850,00
	2	0,00	2.000,00	2.000,00	29.500,00	3.350,00	36.850,00
	3	0,00	2.000,00	2.000,00	29.500,00	3.350,00	36.850,00
	4	0,00	2.000,00	2.000,00	29.500,00	3.350,00	36.850,00
	5	0,00	2.000,00	2.000,00	29.500,00	3.350,00	36.850,00

TOTAL ANUALIDAD 1: 113.850,00 €

TOTAL ANUALIDAD 2: 113.850,00 €

TOTAL ANUALIDAD 3: 113.850,00 €

TOTAL ANUALIDAD 4: 113.850,00 €

TOTAL ANUALIDAD 5: 113.850,00 €

Total = 569.250,00€

List of PI Participants

Nº	Family Name	First Name	Work Institution	Research	Group	Nº of Members
1	VENTO TORRES	MAXIMO	HOSPITAL UNIVERSITARIO Y POLITÉCNICO LA FE	Clinical	Clinical	17
2	CABAÑAS GONZÁLEZ	FERNANDO	HOSPITAL UNIVERSITARIO LA PAZ	Clinical	Clinical	16
3	PALLÁS ALONSO	CARMEN ROSA	HOSPITAL 12 DE OCTUBRE	Clinical	Clinical	18
4	GÓMEZ ROIG	DOLORES	HOSPITAL SANT JOAN DE DEU	Clinical	Clinical	11
5	LLURBA OLIVÉ	ELISA	HOSPITAL VALL D'HEBRÓN	Clinical	Clinical	7
6	LÓPEZ DE HEREDIA GOYA	JON	BIOCRUCES	Clinical	Clinical	10
7	GARCÍA ALGAR	OSCAR	HOSPITAL DEL MAR	Clinical	Clinical	10
8	LÓPEZ HERCE CID	JESÚS	HOSPITAL GREGORIO MARAÑÓN	Clinical	Research	16
9	MARTINEZ MARTINEZ	LEOPOLDO	HOSPITAL UNIVERSITARIO LA PAZ	Basic	Research	5
10	RODRIGUEZ MARTINEZ	GERARDO	HOSPITAL CLINICO UNIVERSITARIO ZARAGOZA	Clinical	Clinical	9
11	MESA GARCÍA	MARÍA DOLORES	UNIVERSIDAD DE GRANADA	Basic	Research	5
12	CABERO PÉREZ	MARÍA JESÚS	HOSPITAL MARQUÉS DE VALDECILLA	Clinical	Research	5
13	LARQUÉ DAZA	ELVIRA	UNIVERSIDAD DE MURCIA	Basic	Research	5

Add PI | Remove PI

Introduction

- Pregnancy, mother and children mortality and morbidities.
- Preeclampsia; Chorioamnionitis; Prematurity
- Intrauterine Growth Restriction
- Hypoxic Ischemic Encephalopathy
- Gut microbiome
- Acute Neurological Disorders in the post-neonatal period.
- Metabolic Syndrome & Epigenetics
- Nutrition

Introduction

PRIMARY OBJECTIVE

- To improve the survival and quality of life of people intervening along the lifespan that goes from the fetal stage of life to the end of growth at the end of adolescence

APPROACH

- Monitoring of pregnancy with early detection of complications (IUGR, Preeclampsia, Chorioamnionitis, toxic substances)
- Avoidance of prematurity and associated complications
- Favoring a smooth fetal to neonatal transition: “gentle approach”
- Enhancing research related to DIAGNOSTIC TOOLS & THERAPY
  - Imaging
  - Biochemical markers
  - Electrophysiology
  - HYPOTHERMIA
  - ANTIOXIDANTS
  - HYPEREXCITABILITY/SEIZURES new drugs
- Enhancing newborn ENVIRONMENT – FAMILY CENTERED CARE, HUMAN LACTATION, MILK BANKING
- SCHOLAR NUTRITION
- SCHOLAR CARE OF SEVERE CONDITIONS
- PROMOTING BASIC RESEARCH IN PRENATAL, PERINATAL AND POSTNATAL AGES with animal models and Randomized clinical trials

Program Objectives

OBJECTIVE 1

To study biomarkers of IUGR, preeclampsia and chorioamnionitis capable of predicting postnatal developmental disorders related to neurocognitive development and nutritional and metabolic status.

OBJECTIVE 2

To study the efficacy of clinical indicators and biomarkers to early predicting neurocognitive and developmental outcomes and identify risk factors for neurologic sequel in children after acute neurologic injuries, and to analyze the effectiveness of diagnostic methods and prevention strategies.

Programme Objectives

OBJECTIVE 3

To study neonatal risk factors for adverse nutritional and metabolic outcomes and possible preventive nutritional strategies.

OBJECTIVE 4

To study pre-and-postnatal environmental factors associated with neurologic, nutritional, and metabolic conditions in the perinatal and childhood periods.

RESEARCH ACTIVITY PROGRAMME
LIST OF WORK PACKAGES

WP Nº	WP TITLE	LEAD PARTIC.Nº	LEAD PARTICIPANT FAMILY NAME	Nº OF RESEARCH.	START DATE/ EVENT	END DATE/ EVENT
1	PRENATAL RISK FACTORS FOR ABNORMAL NEONATAL AND LONG TERM OUTCOME	5	LLURBA OLIVE	20	01/01/2017	31/12/2021
2	NEONATAL RISK FACTORS FOR IMPAIRED NEURODEVELOPMENT OUTCOME	1	VENTO TORRES	20	01/01/2017	31/12/2021
3	NEONATAL RISK FACTORS FOR ADVERSE NUTRITIONAL AND METABOLIC OUTCOME	3	PALLAS ALONSO	20	01/01/2017	31/12/2021
4	POST-NEONATAL RISK FACTORS FOR IMPAIRED NEURODEVELOPMENTAL OUTCOME.	6	LOPEZ-HERCE CID	20	01/01/2017	31/12/2021
5	POST-NEONATAL: RISK FACTORS FOR NUTRITIONAL AND METABOLIC ADVERSE OUTCOME.	11	MESA GARCIA	20	01/01/2017	31/12/2021
6	EPIGENETIC, TOXIC AND ENVIRONMENTAL RISK FACTORS FOR ABNORMAL NEURODEVELOPMENTAL, NUTRITIONAL AND METABOLIC OUTCOME	7	GARCIA ALGAR	20	01/01/2017	31/12/2021

WORKPACKAGE 1

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	1	Start Date/Start Event	01/01/2017		End Date/End Event		31/12/2021
WP TITLE	PRENATAL RISK FACTORS FOR ABNORMAL NEONATAL AND LONGTERM OUTCOME						
PI Family Name	LLURBA	GOMEZ	VENTO	CABAÑAS	PALLAS	LOPEZ DE HEREDIA	GARCIA ALGAR	RODRIGUEZ
Group Nº	5	4	1	2	3	6	7	10
Nº of Resarchers	7	11	17	16	18	10	10	9

OBJECTIVES

Max. 1,200 characters

1.1 To establish a protocol for the diagnosis and obstetrical management of conditions prompting preterm delivery including preeclampsia, IUGR, chorioamnionitis.
1.2 To study the interrelation between epidemiological, toxic, environmental, socio-economic variables and maternal risk factors leading to impairment of neurodevelopment.
1.3 To study the relationship between Doppler hemodynamic compromise of umbilical blood flow and alteration of neurodevelopment.
1.4 To study the interrelation between perinatal complications, postnatal adaptation and neurodevelopment.
1.5 To develop a fetal model of IUGR, to study factor affective fetal growth and test possible preventive and therapeutic strategies.

WORKPACKAGE 1

DELIVERABLES

Brief description and date of delivery — Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained:
1) Protocol for diagnosis and obstetric management of IUGR, chorioamnionites and preeclampsia.
2) Have a register that will include epidemiological, toxic, environmental, and socio-economic variables and maternal risk factors of patients enrolled in the study.
3) Have Doppler hemodynamic variables within a given period of less than 10 days after delivery in 100% of cases and controls.
4) Record of perinatal data in a substantial percentage of study population.
5) Storing of biologic material in Biobank for ulterior study: placental, cord, blood and meconium samples from mothers and newborn infants.
6) Validating biomarkers of infection, vascular reactivity and hypoxia during gestation.
6) Using the animal model for testing different treatments with clinical potential.

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

In WP1, the tasks that will be undertaken will allow to implement a clinical guideline for managing risk pregnancies with IUGR, preeclampsia and fetal hypoxia. Moreover, analysis of biologic materials will contribute to validating valuable biomarkers and the animal model will contribute to increase our knowlede of the physiology and pathophysiology of severe conditions during pregnancy such as IUGR and preeclampsia.

WORKPACKAGE 2

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	2	Start Date/Start Event		01/01/2017		End Date/End Event	31/12/2021
WP TITLE	NEONATAL RISK FACTORS FOR IMPAIRED NEURODEVELOPMENT OUTCOME						
PI Family Name	VENTO	CABAÑAS	PALLAS	LOPEZ DE HEREDIA	GOMEZ	RODRIGUEZ	LLURBA	
Group Nº	1	2	3	6	4	10	5	
Nº of Resarchers	17	16	18	10	11	9	7	

OBJECTIVES

Max. 1,200 characters

1. To analyse the changes in the redox status and oxidative stress in foetal to neonatal transition, the oxidative damage to lipids, neuronal membranes, nitrosative damage, inflammation and damage caused to DNA using UPLC-MS/MS tdeveloped and validated in human biofluids in term and preterm infants.
2. To study the damage to DNA and repair especially in preterm infants.
3. Metabolic changes due to fetal to neonatal transition, oxygen supplementation, hypoxia, hyperoxia, etc. or factors changing Redox status (inflammation, infection, ventilation, etc.) in term and preterm infants.
4. To study neonatal risk factor for brain injury and adverse neurodevelopment in relation to: cerebral oxygenation, transient cardiovascular instability and encephalopathy and prematurity.
5. To develop and integrate data acquisition e-system to validate the development of algorithms to be use of early biomarkers of brain and cardiovascular dysfunction.
6. To enhance the effectiveness of hypothermia in the treatment of hypoxic ischemic encephalopathy with the use of additional therapies such as topiramate or allopurinol.
7. Establish animal models of neonatal hypoxic-isquemic brain injury.

WORKPACKAGE 2

DELIVERABLES

Brief description and date of delivery — Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained:
1) Nomogram of oxygen saturation in the stabilization process at different gestational ages improving the present nomogram.
2) Monitoring of non invasive ventilation using Respiratory Function Monitor to guide caregivers in the delivery room.
3) Clinical guidelines for the management of cerebral oxygenation in the extremely preterm during the transitional stage of movement.
4) Score of biomarkers in the premature circulatory failure, used to direct therapeutic interventions.
4) Score adverse prognostic risk based on analysis of parameters of different integrated monitoring systems.
5) Validation of early predictive biomarkers in biofluids allowing to take clinical decisions at early stages of HIE when MRI imaging is not yet available.
6) Early biomarkers of neuroimaging in preterm infants especially addressing white matter damage (CUS, advanced MRI)
7) Pharmacokinetics, tolerability and toxicity of different experimental treatments in asphyxic neonates undergoing moderate hypothermia.
8) Testing of different treatments with clinical potential in animal models
9) Patent of electronic systems designed.

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

In summary, WP2 aims
(i) to implement a clinical guideline for management of newly born infants in the delivery room avoiding hyper-or-hypoxemia, hemodynamic instability and cardiovascular instability in extremely preterm infants, IUGR newborn infants and post-asphyctic hypoxic-ischemic encephalopathy,
(ii) to enhance the interpretation of aEEG monitoring interpretation to early establish adequate seizure or hyperexcitability or response to medication;
(iii) enhance innovative MRI predictive imaging;
(iv) determine and validate biomarkers of brain damage caused by oxidative stress.
(v) to develop and validate new biomarkers of lipid peroxidation in blood, urine and CSF using UPLC-MS/MS.
(vi) research in "new biomarkers" of hypoxia and brain damage using Untarget QTOF-MS/MS
(vii) neuroimaging biomarkers that early predict white matter damage and prognosis using MRO advanced techniques

WORKPACKAGE 3

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	3	Start Date/Start Event		01/01/2017		End Date/End Event	31/12/2021
WP TITLE	INTERVENTIONS IN THE NEONATAL PERIOD TO ENHANCE ADEQUATE NUTRITION AND METABOLIC OUTCOMES						
PI Family Name	PALLAS	LOPEZ DE HEREDIA	RODRIGUEZ	GOMEZ	LLURBA	CABAÑAS	VENTO
Group Nº	3	6	10	4	5	2	1
Nº of Resarchers	18	10	9	11	7	16	17

OBJECTIVES

Max. 1,200 characters

3.1. Improve neurodevelopment of premature infants by improving nutritional approach which includes:
3.1.1. Generalization of the use of own mother's milk or human donor pasteurized milk
3.1.2. Individualizing fortification
3.1.3. Enhancing the DHA as supplement of the breast milk
3.2 To study the changes experienced by the fresh and pasteurized human milk throughout the technical proccess
3.3 To study the effect of nutritional status at discharge on body composition and glucose intolerance, and on later neurodevelopment.
3.4. To study the effect of pasteurization of donor milk upon the microbiome as compared with non-pasteurized own mothers milk
3.5. To study the quality and composition of different probiotics to assess which one promotes better colonization of the gastrointestinal tract and intestinal development, growth and neurodevelopment. In order to do so microbiome will be analyzed.
3.6.To learn the effect of protein content of the diet on protein synthesis and overall synthesis of certain proteins such as albumin in critical pediatric patient in the Pediatric Intensive Care Unit.

WORKPACKAGE 3

1) Dietary survey. Relation between intake of DHA estimated by survey and longitudinal concentration of DHA. A clinical trial will be launched.
2) Relationship between insulin sensitivity and nutritional status at discharge. Study sample size estimation to evaluate the effect of nutritional status on neurodevelopment.
3) Effect of administered probiotics on intestinal colonization during the initial admission assessed by microbiome analysis. Changes in intestinal colonization of very preterm children during the following months of discharge.
4) Effect of diet on overall protein synthesis on the splanchnic sequestration of amino acids and the synthesis of specific proteins.
5) Comparative table of nutritional losses, immune factors, antioxidants and vitamins of Holder pasteurization and HTST. Clinical guideline on the HTST pasteurization process for use of donated human milk banks.
6) Clinical guideline on the management of mother's milk.
7)Design of an infusion system that incorporates a method of homogenization.

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

The ultimate aim of the present workpackage is to enhance the generalization of the use of own mothers milk and/or human donor milk processed in milk banks with optimized protocols, and assess its beneficial effects studying growth and neurodevelopment in the follow up clinic
In addition, we will evaluate microbiome composition in babies with human milk and with probiotic supplementation and evaluate which composition and dosage of probiotics better influences development of a healthy of microbiome in babies at risk.
We will perform analysis of different compounds, biomarkers, etc, before and after pasteurization using different approaches to verify which is best.
We will develop a dossier of recommendations on the implementation of human milk banks following Good Laboratory Practices.

WORKPACKAGE 4

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	4	Start Date/Start Event	01/01/2017		End Date/End Event	31/12/2021
WP TITLE	POST-NEONATAL RISK FACTORS FOR IMPAIRED NEURODEVELOPMENTAL OUTCOME.					

PI Family Name	LOPEZ-HERCE	LOPEZ DE HEREDIA	CABERO	MARTINEZ	PALLAS	MESA	LARQUÉ	
Group Nº	8	6	12	9	3	11	13	
Nº of Resarchers	16	10	5	5	18	5	5	

OBJECTIVES

Max. 1,200 characters

4.1 To identify populations and postnatal risk factors for major neurodevelopmental impairment and neurological disorders in childhood.
4.2. To study the usefulness of methods for early detection of risk factors and neurological disorders: Neuroimaging methods: ultrasound, CT, MRI, PET, cerebral blood flow, NIRS, EEG, Biochemical biomarkers. Maturation of circadian rhythms.
4.3. To study the efficacy of prevention and treatment methods to reduce neurological disorders,/.Oxygenation: to analyze the influence of the fraction of inspired oxygen during cardiopulmonary resuscitation and treatment of hypoxic-ischemic alterations in the development and prevention of acute neurological injury.
4.4 To develop animal models of diagnosis, prevention and treatment of neurological diseases that occur in pediatric animal models of hypoxic neurological injury, ischemic neurologic injury and cardiac arrest.
4.5. To establish the association between oxidative, inflammatory and endothelial risk factors related to aetiology of autism spectrum.
4.6. To examine the effects of nutrition and physical exercise on cognition an

WORKPACKAGE 4

DELIVERABLES

Brief description and date of delivery — Max. 1,500 characters

1) Multicenter study of neurological disorders in children with: cardiac arrest, congenital heart disease, cardiac surgery and stroke. 2) Clinical guidelines for neuroimaging studies in children at risk of acute neurological disorders: measurements of cerebral blood flow, oxygen saturation by NIRS, EEG and brain damage biomarkers in children with risk of neurological disorders. 3) Clinical guidelines for FiO2 during cardiopulmonary and respiratory rate during cardiopulmonary resuscitation.4) Multicenter study protocol of hypothermia after cardiac arrest in children, and potentially neuroprotective drugs during hypoxia-ischemia and biomarkers of neurodevelopment damage in childhood to raise future clinical studies. 5) Pediatric animal model for brain damage of different etiologies including reports of the alterations of cerebral blood flow and saturation by NIRS,and biomarkers of oxidative stress. Experimental study protocol of the influence of FiO2 in pediatric cardiac arrest. Experimental study protocol of the influence of respiratory arrest in pediatric cardiac arrest. 6) Children diagnosed autism spectrum disorder will be compared with healthy children of the same age. Plasmatic inflammatory and oxidative stress biomarkers will be assessed in order to find a possible related pathogenic mechanism. 7) Develop a 5-months exercise program and effectiveness assessed with cutting edge technology to assess cognitive performance, brain structure and function (EEG; MRI)

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

In summary, a clinical guideline will be proposed for the early management of the various disorders that can cause brain damage (stroke, cardiac surgery, infections, hypoxia ischemia, autism spectrum disorders, obesity) including validation of circadian index function with other traditional tests as potential predictor of neurodevelopment.

WORKPACKAGE 5

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	5	Start Date/Start Event		01/01/2017		End Date/End Event	31/12/2021
WP TITLE	POST-NEONATAL RISK FACTORS FOR NUTRITIONAL AND METABOLIC ADVERSE OUTCOME						
PI Family Name	MESA	LARQUE	GOMEZ	LLURBA	GARCIA ALAGAR	LOPEZ-HERCE	CABERO	PALLAS
Group Nº	11	13	4	5	7	8	12	3
Nº of Resarchers	5	5	11	7	10	16	5	18

OBJECTIVES

Max. 1,200 characters

5.1 To investigate subclinical cardiovascular disease in children 8-10 years old, with perinatal developmental factors (IUGR or extreme low birth weight) that potentially influences the future risk of this disease.
5.2. To define non-invasive approaches to identify children with early changes in cardiovascular physiology that potentially affect future cardiovascular outcome, emphasizing their potential applications in childhood.
5.3 To evaluate the biological effects of early and realistic interventions in the selected population, analyzing potential changes in the defined biomarkers.
5.4 To investigate the influence of genetic variants on the development of obesity and yo evaluate the association between those genetic variants and food habits, physical activity and biomarkers of inflammation, cardiovascular diseases risk and oxidative stress.
5.5 To establish the association between nutrition and physical exercise on metabolic outcomes in overweight/obese children.

WORKPACKAGE 5

DELIVERABLES

Brief description and date of delivery — Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained:
1) Epidemiology of X syndrome and report on the contributing factors: maternal, genetic variants as determined by next generation sequencing in the development of obesity. Results from the case-control study.
2) Report on the relationship between genetic variants, food habits, physical activity and biomarkers of inflammation and oxidative stress upon cardiovascular diseases with special emphasis on hypertension.
3) Report on the noninvasive (echocardiography) cardiovascular measurements and its correlation within the cardiovascular diseases risk factors.
4) Strict periodical Holter control of blood pressure in patients at risk.
5) Report on the efficacy of the intervention in terms of cardiovascular diseases risk factors reduction.

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

Our Work Package seeks to early identify patients at risk to develop metabolic syndrome in the perinatal period. The protocol of early identification will include perinatal factors affecting the mother, the fetus and the newborn. The application of the protocol will allow to establish an epidemiological frame and score for patients at risk. Concomittantly, patients at risk will be studying using genetic and metabolomic platforms, and non-invasive cardiovascular tools (ecocardiography), and monitor of insulin resistance and hypertension.
As a consequence a protocol to define and to prevent metabolic syndrome in children by the use of early biomarkers will be put foward. This protocol will be defined by consensus and based in our results.

WORKPACKAGE 6

DESCRIPTION OF EACH WORKPACKAGE

WP Nº	6	Start Date/Start Event		01/01/2017		End Date/End Event	31/12/2021
WP TITLE	EPIGENETIC, TOXIC AND ENVIRONMENTAL RISK FACTORS FOR ABNORMAL NEURODEVELOPMENTAL, NUTRITIONAL AND METABOLIC OUTCOME						
PI Family Name	GARCIA ALGAR	RODRIGUEZ	GOMEZ	CABAÑAS	PALLAS	VENTO	MESA	LARQUE
Group Nº	7	10	4	2	3	1	11	13
Nº of Resarchers	10	9	11	16	18	17	5	5

OBJECTIVES

Max. 1,200 characters

6.1. Development of analytical methodology to describe and validate biomarkers of prenatal and postnatal exposure to substances and drugs of abuse, drugs of prescription, persistent organic toxics and heavy metals in different alternative matrix.

6.2 To study the prevalence of prenatal and postnatal exposure these several substances on prospective and retrospective cohorts of newborn infants born in different regions of Spain, and to perform follow-up of the cohorts of prenatally exposed newborns.

6.3 To develop animal models of prenatal exposure to xenobiotics, mainly alcohol to define biomarkers of different substances (parent substances and metabolites) to which foetus, newborn, child and adolescent can be exposed

WORKPACKAGE 6

DELIVERABLES

Brief description and date of delivery — Max. 1,500 characters

After reaching these tasks, the following outputs will be obtained:
1) List, detection time window, analytical methodology, significance and importance, and applicability of the alternative matrices.
2) List and table of biomarkers (parent substance, metabolites) of exposure of different substances.
3) Description of the analytical methodologies and its applicability.
4) Prevalence figures of prenatal and postnatal exposure to several substances.
5) Clinical and analytical results derived from the follow up of several substances prenatal and postnatal exposure.
6) Pharmacokinetic results and prescription recommendations and indications of medicines in children.
7) Description of animal models of prenatal exposure to several substances.

MILESTONES

Brief description and date of achievement — Max. 1,500 characters

The present Work Package aims to establish a comprehensive map of toxics (legal/no legal) to which our newborn infants are exposed. In addition, our knowledge of the reality will allow to implement clinical guidelines for the identification and treatment in the perinatal period (pregnancy and newborn period) of the consequences of drug exposure of the mother and fetus. In addition, analytical methods for the identification and grading of exposure will be validated. Matrixes used will imply biofluids from the mother including breast milk, and from the babies.
Guidelines for future parents and for the Community will be developed.

DELIVERABLES

DELIV. Nº	DELIVERABLE NAME	WP Nº	LEAD PARTICIPANT FAMILY NAME	DISSEMINANTION LEVEL	DELIVERY DATE
1	Protocol for diagnosis and obstetric management of IUGR, chorioamnionitis and preeclampsia including echography, Doppler and biomarkers.	1	GOMEZ	Public	31/12/2019
2	Provide epidemiological, toxic environmental, socio-economic variables and maternal risk factors of patients enrolled in the study. Store biomaterial (placenta, cord, blood, etc.,) in Biobank for ulterior study.	1	GOMEZ	Public	31/12/2021
3	Guidelines for the management of arterial and brain oxygenation, and respiratory function in the extremely preterm during the fetal to neonatal transition and postnatal adaptation.	2	VENTO	Public	31/12/2020

DELIVERABLES

4	Development and validation of oxidative stress and metabolic biomarkers in the premature circulatory failure to guide therapeutic interventions.	2	VENTO	Public	31/12/2018
5	Elaboration of scores of risk of impaired neurocognitive outcome based on the analysis of clinical, analytical and metabolic parameters of different integrated monitoring systems and analytical procedures.	2	VENTO	Public	31/12/2019
6	Protocols of implementation of the use of own mothers milk and human donor milk in the NICU and probiotics on nutritional outcomes, NEC, late onset sepsis and microbiome composition.	3	PALLAS	Public	
7	Effect of individualized fortification and protein supplementation on overall protein synthesis and synthesis of specific proteins. Comparative table of nutritional losses, immune factors, antioxidants and vitamins of Holder pasteurization and HTST.	3	PALLAS	Public	

DELIVERABLES

8	In Pediatric Intensive Care Unit Effect of protein content in parenteral nutrition upon the overall protein synthesis on the splanchnic sequestration of amino acids and the synthesis of specific proteins.	3	PALLAS	Public	
9	Multicenter study in Pediatric Intensive Care Units of a comprehensive protocol of neurological disorders in children with: cardiac arrest, congenital heart disease, cardiac surgery and stroke.	4	LOPEZ HERCE	Public	
10	Clinical Guidelines recommendation for the use and interpretation of measurements of cerebral blood flow, cerebral saturation measured by NIRS, EEG and brain damage biomarkers in children with risk of neurological disorders.	4	LOPEZ HERCE	Public	

DELIVERABLES

11	Development, validation and research of pediatric animal models for ischemic neurological damage, for hypoxic neurological damage, and for cardiac arrest.	4	LOPEZ HERCE	Public	
12	Next generation sequencing, mass spectrometry metabolites, and clinical studies on the influence of genetic variants on the development of X syndrome including obesity, insulin resistance and hypertension in babies with risk factors in the perinatal period (e.g.: IUGR, extreme prematurity, mother with > BMI). Correlation with social and nutritional habits.	5	MESA	Public	
13	Efficacy of consensus guidelines including diagnosis and clinical management upon cardiovascular diseases using non invasive methods such as ecocardiography, Holter monitorization of blood pressure, diet and exercise in infancy and scholar ages in a cohort of at risk babies.	5	MESA	Public	

DELIVERABLES

14	Efficacy of consensus guidelines including diagnossi and clinical management upon obesity and insulin resistance using validated metabolic stress tests and biomarkers in infancy and scholar ages in a cohort of at risk babies.	5	MESA	Public	
15	In alternative matrices (hair meconimu, blood, urine) especially suitable for newborn infants to establish a list of legal and non legal toxics to which the pregnant mother, the fetus and the newborn (breast-feeding) have been exposed, optimal detection time frame, most suitable analytical methodology (e.g.: mass spectrometry, QTOF), relevance and applicability.	6	GARCIA ALGAR	Public	
16	Development, validation and description of the most suitable analytical methodologies and its applicability; epidemiological studies to assess prevalence figures of prenatal and postnatal exposure to several substances (legal and non legal) and include a pharmacokinetic and pharmacodyamic study of common drugs prescribed to the mother during gestation.	6	GARCIA ALGAR	Public	
17	Development of animal models of prenatal exposure to several substances (zebra fish, mice, rats) and implementation of analytical methods in tissue non available in clinical setting to optimize reliability of clinically applied methods.	6	GARCIA ALGAR	Public	

MILESTONES

MILESTONE Nº	MILESTONE NAME	WP Nº	DUE DATE	MEANS OF VERIFICATION
1	Clinical guideline for managing risk pregnancies with preeclampsia, IUGR, or chronic fetal hypoxia.	1	31/12/2019	Published guidelines and peer reviewed papers.
2	Optimization of stabilization during fetal to neonatal transtion of preterm infants using an individualized approach for oxygenation and ventilation, and establish ranges of normality of specific biomarkers, neuroimaging and electrophysiology parameters and complementary drugs to hypothermia in hypoxic-ischemic encephalopathy.	2	31/12/2020	Published peer reviewed papers. Guidelines published by the Spanish Neonatal Society.
3	To develop a dossier of recommendations on the generalization of the use of human milk in the NICU, relevance and interventions in the MILK BANKS following Good Laboratory Practice, and establish the optimal Probiotic and its effects upon microbiome and NEC	3	31/12/2021	Scientific and technical reports. Microbiological Information. Peer reviewed scientific papers.
4	Clinical guideline will be proposed for the early management of the various disorders that can cause brain damage.	4	31/12/2021	International Consensus Guidelines. Peer reviewed scientific papers. Available data base
5	Protocol to define and to prevent metabolic syndrome in children by the use of early biomarkers. This protocol will be defined by consensus and based in our results.	5	31/12/2021	Cohort information at 3-4 years of age after implementation of the clinical guidelines. Peer reviewed scientific papers.
6	Presentation of clinical guidelines, for example, human milk banks, and environmental toxic (legal and non legal drugs).	6	31/12/2021	Basic and clinical scientific papers. Toxicological Guidelines for the Perinatal Periods by the Health Ministry of Spain.

MANAGEMENT STRUCTURE

PROGRAMME 1 COORDINATOR
(NETWORK COORDINATOR)
M Vento

ASSISTANT MANAGER
A Tenería

SCIENTIFIC ASSISTANTS
OMIC platforms
Statistical assistant
(TBD)

GROUP LEADERS
Assigning specific scientist specific tasks
Request deadlines
Perform local meetings to promote discussion

FUNCTIONAL STRUCTURE

CLINICAL EPIDEMIOLOGICAL

- Obstetrics
- Neonatologists
- Intensivists
- Consultants

Recruitment
Electronic Data sheet
Ethics Committee
Storing images
Centralizing statistics

ANALYTICAL

- MS/MS platforms
- Genetic/Epigenetic
- Transcriptomics
- Lipidomics
- Microbiome

EXPERIMENTAL

- Animal models devoted to implement clinical studies

OBJECTIVE 1

Programme:	Interventions during pregnancy, neonatal period, and pediatric age for prevention and treatment of conditions influencing adult health.
OBJECTIVES INCLUDED	EXPECTED IMPACTS
To study biomarkers of Intrauterine Growth Retardation, preeclampsia and chorioamnionitis capable of predicting postnatal developmental disorders related to neurocognitive development and nutritional and metabolic status.	National and International Guidelines to early diagnose and treat Preeclampsia, IUGR and chorioamnionitis. Follow up programs to study the consequences of these conditions upon neurocognitive development until school age. Further development of biomarkers and ultrasound techniques in the field of Obstetrics Improvement of survival free of major complications of IUGR infants. Scientific peer reviewed papers

OBJECTIVE 2

Programme:	Interventions during pregnancy, neonatal period, and pediatric age for prevention and treatment of conditions influencing adult health.
OBJECTIVES INCLUDED	EXPECTED IMPACTS
	Scientific peer reviewed papers
To study biomarkers capable of early predicting postnatal neurocognitive and developmental outcomes and identify risk factors for an altered postnatal development in children, and establish a correlation between biomarkers and the effectiveness of diagnostic methods and prevention strategies.	New protocols for individualized preterm stabilization in the delivery room. Randomized controlled trials to enhance the effectiveness of hypothermia in hypoxic-ischemic encephatolopathy using additional strategies. Development of cot-side diagnostic and prognostic biomarkers leading to patents, spin off enterprises. Improvement of diagnostic and therapy in the clinical setting Scientific peer reviewed papers

OBJECTIVE 3

Programme:	Interventions during pregnancy, neonatal period, and pediatric age for prevention and treatment of conditions influencing adult health.
OBJECTIVES INCLUDED	EXPECTED IMPACTS
To study neonatal risk factors for adverse nutritional and metabolic outcomes and possible preventive nutritional strategies.	Generalization of the use of human milk, milk banking, individualized fortification in preterm infants in the NICU Studies on the effectiveness of probiotic and/or DHA supplementation and pasteurization methods in the milk banks. Microbiome. Epidemiology of risk factors in mother, fetus, newborn and infants to early develop X syndrome. Protocols of nutritional and medical interventions to diagnose infants at risk, and to improve outcomes. Genetic studies to unravel genes related to the development of obesity, resistance to insulin, hypertension. Studies on the influence of the protein content in parenteral nutrition and outcomes in the PICU. Scientific peer reviewed papers.

OBJECTIVE 4

Programme:	Interventions during pregnancy, neonatal period, and pediatric age for prevention and treatment of conditions influencing adult health.
OBJECTIVES INCLUDED	EXPECTED IMPACTS
To study pre-and-postnatal environmental factors associated with neurologic, nutritional, and metabolic conditions in the perinatal and childhood periods.	Epidemiology of exposure to legal and illegal toxics by pregnant women and offspring. Guidelines informing on the risks of exposure to legal and illegal toxic substances. Pharmacokinetics and Pharmacodynamics of commonly used drugs and abuse substances in th perinatal period Development of new diagnostic biomarkers and tools. Research on matrices capable of unravel time and intensity of exposure to legal and illegal drugs. Animal models to study the teratogenic consequences of specific legal and illegal substances. Scientific peer reviewed papers.

NUESTRO OBJETIVO en RED

- Implicar a los distintos grupos en proyectos relacionados con los **objetivos comunes** mediante la cumplimentación de los **working packages** y la producción de **deliverables** que se puedan probar al ISCIII al finalizar el 3er año de RD16.

- En esta tarea tiene que ser coordinada por el Coordinador Nacional, el Asistente al Coordinador y sobre todo los Líderes de los Grupos que al diseñar los estudios deben tener en cuenta la estructura de Red.

- La comunicación entre los distintos niveles debería ser fluida.

- Ello se facilitará con la incorporación de los grupos a ensayos multicéntricos con objetivos comunes.