15 PhD Fellowship positions available in the Marie Skłodowska-Curie actions Innovative Training Network "TREATMENT" (H2020-MSCA-ITN -721236)

European Training Network: Metabolic Dysfunctions associated with Pharmacological Treatment of Schizophrenia

Located in
Spain, Portugal, Sweden, Israel, Ireland, and Slovenia.

Project background and goal: TREATMENT is a Marie Sklodowska Curie Innovative Training Network proposal directly addressing the need for high-level training and career paths in risk evaluation of drug induced metabolic dysfunctions, a relevant aspect, so far unexplored by traditional toxicology studies, but urgently needed to challenge current severe limitations of health care interventions in mental disorders. These patients require life-long medications that subsequently trigger metabolic diseases with a strong negative impact on their health and well-being. To achieve this, and improve adherence to treatments, we will evaluate how short-term antipsychotic drug responses impact long-term metabolic control to identify and validate biomarkers with clinically predictive value for targeting drug induced metabolic dysfunctions. This effort will have added commercial value by enabling the design of predictive marker kits for testing adverse secondary metabolic effects of drugs to be used in pharmacological and medical practice. TREATMENT will provide multidisciplinary knowledge, capabilities and tools to implement this ambitious strategy by the training of young scientists in a program that combines pharmacology, metabolism and mental health research with strategies for product and tool design and validation. Our ultimate goal is to empower the intersectorial and trans-national employability of young scientists across academic, public and private sectors to foster the development and implementation of personalized medicine tools that will provide effective treatment regimens for life long health-care interventions and decrease the risk for development of chronic metabolic diseases.

Career Stage
Early Stage Researcher (ESR) or 0-4 yrs. (Post Graduate)
Qualifications required for entry into the PhD program in each partners country can be found on each partners website or by contacting the partner by email (see links in the project descriptions section)**. Completion of a Master Programme is not required for application but, the applicants should have a Master degree granted before the 30th of September, 2017.**

Benefits and salary
The MSCA programme offers a highly competitive and attractive salary and working conditions. The successful candidates will receive a salary in accordance with the MSCA regulations for early stage researchers. Exact salary will be confirmed upon appointment [Living Allowance = 3110 €/month (correction factor to be applied per country) + mobility allowance = 600 €/month. Researcher's may also qualify for a family allowance of 500 €/month depending on the family situation].

In addition to their individual scientific projects, all fellows will benefit from further continuing education, which includes scientific skills courses, transferable skills courses, as well as active participation in workshops and conferences and the opportunity to go on secondments to partner labs.

Applicants need to fully comply with the three eligibility criteria:

1) **Early-stage researchers** (ESR) are those who are, at the time of recruitment by the host, in the first four years (full-time equivalent) of their research careers. This is measured from the date when they obtained the degree which formally entitles them to embark on a doctorate, either in the country in which the degree was obtained or in the country in which the research training is provided, irrespective of whether or not a doctorate was envisaged. Please note applicants cannot already hold a PhD.
2) **Conditions of international mobility of researchers**: Researchers are required to undertake trans-national mobility (i.e. move from one country to another) when taking up the appointment. At the time of selection by the host organisation, researchers must not have resided or carried out their main activity (work, studies, etc.) in the country of their host organisation for more than 12 months in the 3 years immediately prior to their recruitment. Short stays, such as holidays, are not taken into account.
3) **English language**: Network fellows (ESRs) must demonstrate that their ability to understand and express themselves in both written and spoken English is sufficiently high for them to derive the full benefit from the network training.

Application procedure:

All applications must be made on the TREATMENT APPLICATION FORM https://www.iib.uam.es/anuncios/
This form should be completed and emailed to itn-treatment@listas.iib.uam.es by 5.00pm on 28th February 2017. The email should clearly state your top three projects in order of preference (e.g., 1ST ESR8, 2nd ESR1 and 3rd ESR5).

Eligible applications will be forwarded to the relevant partners in charge of each project and each partner will shortlist their applicants and conduct interviews from mid-April to mid-May. Applicants will be informed of the outcome by end of May 2017 (timelines may vary a little between partners). Successful applicants will need to prove that they are eligible (three aspects: respect ESR definition, mobility criteria, and English language proficiency). The selected ESRs are expected to start May-Sep. 2017.

PhD Projects

ESR1 will analyze tissue-specificity of schizophrenia and antipsychotic drugs on insulin sensitivity *in order to unravel the tissue specificity of the critical nodes of insulin signalling that are dysregulated by the schizophrenia per se or as a consequence of the impact of the pharmacological treatment with olanzapine/aripriprazol catabolism on whole body metabolic control.*

The ESR will examine the selective modulation of the critical nodes of insulin signalling (IR, IRS1/2, PTP1B, Akt) during schizophrenia *per se* and under antipsychotic therapy and the impact on whole body glucose homeostasis and energy expenditure. We expect to find differences in insulin-sensitive cells and tissues from mice treated with drugs for short or long time-periods. Secondly, the ESR will conduct studies in genetically modified (GM) mice bearing tissue-specific insulin resistance (IRS2 KO) or hypersensitivity (PTP1B KO). This approach will be relevant for the design of combined therapies aimed to ameliorate metabolic disturbances linked to antipsychotic treatments.

Host: Instituto de Investigaciones Biomédicas "Alberto Sols", IIBm (CSIC-UAM).
Supervisors: Professor Ángela M. Valverde and Dr. María Monsalve (For information on this lab and more detail of the project please see https://www.iib.uam.es/portal/ and contact avalverde@iib.uam.es or mpmonsalve@iib.uam.es).

ESR2 will study the effect of antipsychotic drugs in the pancreas *in order to analyze the impact of schizophrenia per se and its pharmacological treatment with olanzapine or aripiprazol in the molecular machinery that modulates the endocrine pancreas.*

The ESR will study the effects of schizophrenia *per se* and its treatment with antipsychotic drugs in the endocrine pancreas. By using cellular models of pancreatic alpha and beta cells, we expect to unravel alterations in the molecular mechanisms of insulin/glucagon secretion and cell plasticity due to antipsychotic drugs. It is expected to find altered responses to gastrointestinal peptides, particularly GLP1R agonists. In the *in vivo* mouse models of schizophrenia or its pharmacological treatments, the ESR will analyse if and how islet morphometry may be altered together with increased ER stress (PERK, ATF6, IRE1α) and apoptosis (Bax/Bak, caspase-3), limiting the first and second phase of insulin secretion.

Host: Instituto de Investigaciones Biomédicas "Alberto Sols", IIBm (CSIC-UAM).
Supervisors: Professor Ángela M. Valverde and Professor Francisco Abad (For information on this lab and more detail of the project please see https://www.iib.uam.es/portal/ and contact avalverde@iib.uam.es or francisco.abad@salud.madrid.org).

ESR3 will evaluate Drug-induced mitochondrial dysfunction *to unravel how antipsychotic drug catabolism in the liver alters mitochondrial activity, and how the ensuing modified activity of master transcriptional regulators controlling oxidative metabolism may led to general metabolic dysfunctions including fibrosis.*

The ESR will study drug specific differences on mitochondrial activity, as well as different capacity of the model animals to cope with the alterations in mitochondrial activity. The ESR will analyse background and drug specific differences in the induction of mitochondrial biogenesis (PGC1α/β, TFAM, SIRT3) as a compensatory response of the liver to mitochondrial dysfunction and in the capacity to fully recover mitochondrial function that if limited, would result in the accumulation of dysfunctional mitochondria and elevated ROS. The final aim of the study would be to determine how these limitations in the mitochondrial oxidative capacity contribute to long term metabolic dysfunctions following chronic drug administration.

Host: Instituto de Investigaciones Biomédicas "Alberto Sols", IIBm (CSIC-UAM).
Supervisors: Dr. María Monsalve and Dr. Juan Cigudosa (For information on this lab and more detail of the project please see https://www.iib.uam.es/portal/ and contact mpmonsalve@iib.uam.es or jccigudosa@nimgenetics.com).

ESR4 will analyze the role of mitochondrial dysfunction in drug-induced cardiovascular disease *in order to evaluate to what extent drug induced mitochondrial dysfunction may result in the development of cardiovascular disease.*

The ESR will evaluate the genetic basis for variability on drug induced mitochondrial dysfunction on cardiovascular disease. Mitochondrial dysfunction is associated with cardiovascular disease, hence the putative impact of drug induced mitochondrial dysfunction on the cardiovascular system will be studied analyzing both macrovascular and microvascular complications. To that end the ESR will test the effects of psychotropic drugs on endothelial dysfunction, atheroma plaque formation, angiogenesis and retinopathy.

Host: Instituto de Investigaciones Biomédicas "Alberto Sols", IIBm (CSIC-UAM).
Supervisors: Dr. María Monsalve and Professor Santiago Lamas (For information on this lab and more detail of the project please see https://www.iib.uam.es/portal/ and contact mpmonsalve@iib.uam.es or slamas@cbm.csic.es).

ESR5 will study the effects of the antipsychotic drugs on human adipose tissue insulin signalling, glucose and lipid metabolism.

The ESR will: i) Investigate the in vitro effects on glucose uptake in human adipose cells and its interactions with insulin signalling. ii) Elucidate the effects on lipolysis, lipid storage and the expression genes regulating lipid metabolism (including fatty acid synthesis and storage as well as oxidation).

The ESR will analyse alterations in insulin-stimulated glucose uptake, insulin signalling and lipid handling that may contribute to the development of insulin resistance following antipsychotic drug treatment. These may contribute to lipid deposition in other organs, such as liver and muscle, leading to dyslipidemia. These studies will provide biomarkers on drug induced metabolic dysfunction of the adipose tissue.

Host: Uppsala Universitet (Uppsala, Sweden)
Supervisors: Professor Jan Eriksson and Professor Angela M. Valverde (For information on this lab and more detail of the project please see http://katalog.uu.se/profile/?id=N13-487 and contact jan.eriksson@medsci.uu.se or avalverde@iib.uam.es).

ESR6 will study drug-induced low-grade chronic inflammation in human adipose tissue including interaction with other tissues *in order to investigate effects of antipsychotic drugs on adipose tissue hormones, adipokines and chemochines, inflammatory markers, and other factors of potential importance for the development of T2D and obesity.*

Human volunteers will have short term drug treatment, and in vivo and in vitro analyses will be performed., Assessments will include changes in hormonal (adipokines, dopamine, cortisol) and inflammatory factors, eg lipid species (fatty acid profiles, eicosanoids, leukotrienes), cytokines (eg TNFα, IL6, IL1β) and immune cells in adipose tissue. These factors may contribute to low-grade systemic inflammation, changes in macrophage polarization, whole body insulin resistance, liver steatosis and pancreatic beta cell dysfunction. Furthermore, samples from healthy, prediabetic and type 2-diabetes subjects will be compared, to identify putative differences in the drug effects depending on the metabolic milieu.

Host: Uppsala Universitet (Uppsala, Sweden).
Supervisor: Professor Jan Eriksson (For information on this lab and more detail of the project please see http://katalog.uu.se/profile/?id=N13-487 and contact jan.eriksson@medsci.uu.se).

ESR7 will evaluate the integrative metabolic effects of antipsychotic treatment in a rat model *in order to evaluate global alterations in metabolic fluxes induced by in vivo treatment with olanzapine or aripiprazol in a rat model.*

The ESR will develop non-invasive methods for characterizing hepatic expression of albumin, ApoB100, ApoJ and PON-1 and to apply these to rats treated with anti-schizophrenic drugs. The ESR will aim to integrate these methods with established stable isotope tracer protocols for characterizing changes in intermediary metabolic fluxes in the rat model administered with anti-schizophrenic drugs. The ESR will evaluate alterations in the insulin-signalling pathway (IR, IRS1/2, AKT) in isolated fat cells, BAT, muscle and skin. The ESR will identify the best set of biomarkers (plasma and urinary metabolites/proteins) that are correlated with changes in drug-induced metabolic fluxes and changes in activation of insulin signalling mediators at the level of these tissues. Finally, the ESR will validate the predictive efficacy of these biomarkers with the development of insulin resistance and cardiovascular disease in a population of anti-schizophrenic drug users.

Host: Centre for Neuroscience and Cell Biology, CNC (Coimbra, Portugal).
Supervisors: Dr. John Jones and Dr. Eugenia Carvalho (For information on this lab see http://www.cnbc.pt/research/department_show.asp?iddep=1138 and for more project detail please contact john.griffith.jones@gmail.com or eugeniamlcarvalho@gmail.com).

ESR8 will study the metabolic impact of antipsychotic drugs on the CNS and in the regulation of whole body metabolism (hypothalamic-periphery axis) *in order to evaluate the alterations in behaviour and in hypothalamic neurogenesis, as well as the effects on glucose and lipid metabolism in peripheral tissues after in vivo treatment with olanzapine or aripiprazol in rodents.*

The ESR will study the two different models of schizophrenia, the transgenic mouse DISC1 and the neurodevelopmental rat model of neurogenesis disruption with prenatal administration of the cytostatic agent methylazoxymethanol (MAM). Besides behavioral and neurogenic alterations, we will evaluate insulin action in the CNS and peripheral tissues. The ESR will measure insulin-stimulated 14C-glucose uptake and lipolysis in isolated fat cells. In addition, the ESR will use High resolution respirometry to study mitochondrial respiration as well as cellular "fitness" in BAT, WAT, skeletal muscle and the different isolated brains regions. The ESR will identify altered pathways in the CNS that may correlate with the changes observed in the periphery and validate the findings through human studies on antipsychotic drugs.

Host: Centre for Neuroscience and Cell Biology, CNC (Coimbra, Portugal).
Supervisor: Dr. Eugenia Carvalho (For information on this lab see http://www.cnbc.pt/research/department_show.asp?iddep=1138 and for more project detail please contact eugeniamlcarvalho@gmail.com).

ESR9 will evaluate Drug-induced activation of the Unfolded Protein Response (UPR) in the liver *in order to explore the effects of olanzapine/aripriprazol on ER stress signalling in the liver and whether mitochondrial UPR is activated by the drugs; to find molecular connections between drug catabolism and ER stress responses in the liver* in vitro *and* in vivo.

The ESR will aim to delineate molecular interconnectivities between drug catabolism and the extent of UPR (PERK, ATF6, IRE1α) in the liver. This will be achieved by testing the drug effects in the ER stress responses in genetically modified hepatocytes by CRISPR/Cas9 editing followed by the study of their metabolic responses. Animals with liver specific impaired UPR will be evaluated.

Host: Hebrew University Jerusalem Israel, HUJI (Jerusalem, Israel).
Supervisors: Professor Boaz Tirosh and Professor Afshin Samali (For information on this lab and more detail of the project please see http://medicine.ekmd.huji.ac.il/en/publications/researchersPages/pages/boazt.aspx and contact boazt@ekmd.huji.ac.il or afshin.samali@nuigalway.ie).

ESR10 will study the effects of antipsychotic drugs in the immune system *in order o characterize alterations in the immune system in schizophrenia and following olanzapine/aripriprazol treatment.*

The ESR will examine the direct effect of the antipsychotic drugs on immune cell activation in vitro in co-culture settings, as well as the secondary response of the immune system to hepatic drug catabolism in vivo. The lymphocyte/macrophage infiltration into liver and adipose tissues following antipsychotic treatment will also be evaluated in animal models of schizophrenia as well as metabolic dysfunctions. Considering the association between the immune responses with obesity and metabolic adaptations, we should establish the cause-effect relationships between the innate and chronic immunity with drug induced metabolic dysfunctions using mice that are immunodeficient.

Host: Hebrew University Jerusalem Israel, HUJI (Jerusalem, Israel).
Supervisors: Professor Boaz Tirosh and Professor Afshin Samali (For information on this lab and more detail of the project please see http://medicine.ekmd.huji.ac.il/en/publications/researchersPages/pages/boazt.aspx and contact boazt@ekmd.huji.ac.il or afshin.samali@nuigalway.ie).

ESR11 will analyze the interferences of antipsychotic drugs on hepatocyte adaptive responses that determine loss of function, compromised survival and induction of fibrosis *in order to determine how the drugs alter the adaptive responses of liver cells and how they impact hepatocyte functionality and their capacity to survive in response to stressors.*

The ESR will test the acute effect of antipsychotic drug treatment on primary hepatocytes and liver slices Rats treated with antipsychotic drugs will be used to investigate how the putative loss in hepatocyte functionality impacts on the induction of steatosis, fibrosis and steatohepatitis and evaluation of increased liver sensitivity to damage. To establish the links between the short-term impairement of hepatic functionality following drug administration with long-term enhanced sensitivity to liver stressors, likely to be associated with increased liver fat accumulation and development of fibrosis.

Host: Univerza V Ljubljani, UL (Ljubljani, Slovenia).
Supervisor: Professor Irina Milisav (For information on this lab and more detail of the project please see http://www.mf.uni-lj.si/en/index.html or contact irina.milisav@mf.uni-lj.si).

ESR12 will evaluate the polymorphisms associated with antipsychotic responses *in order to identify patients that under antipsychotic treatment could develop alterations on glucose and lipid metabolism.*

The ESR will use pharmacogenetics to predict which patients will respond and who will develop the metabolic syndrome. Particularly, we aim 1) To identify polymorphisms associated to metabolic syndrome after antipsychotic administration 2) To identify possible drug targets. The ESR will identify polymorphisms associated to metabolic syndrome induced by antipsychotics. This will allow the establishment of genetic biomarkers to predict drug response. Genotyping patients before treatment will help physicians to decide therapy.

Host: Fundación para la Investigación Biomédica del Hospital Universitario La Princesa, FIBHUP (Madrid, Spain).
Supervisor: Professor Francisco Abad (For information on this lab and more detail of the project please see http://www.iis-princesa.org/infraestructuras/unidad-de-investigacion-clinica/ or contact francisco.abad@salud.madrid.org).

ESR13 will carry out a translational Integrative genomic analysis on human patients samples using bioinformatic strategies.

The ESR will study the genomic and expression profiles of a cohort of patients and controls where short term responses to antipsychotic administration have been studied by other participant groups. ESR13 will characterize the different genomic patterns that predict long term metabolic side effects in human patients with the purpose of designing predictive tests for personalized medicine in antipsychotic treatment. The design of a rapid, economic and reliable predictive test for quantification of parameters that predict long-term metabolic dysfunctions that may result from chronic drug administration will be useful for application on diagnosis and follow up of schizophrenic patients and/or other related pathologies.

Host: NIMGenetics, Genómica y Medicina S.L., NIMGenetics (Madrid, Spain), (company).
Supervisor: Dr. Juan Cigudosa (For further information on the company see https://www.nimgenetics.com/ or contact jccigudosa@nimgenetics.com).

ESR14 will study of the pathological metabolic adaptations in the CNS in response to antipsychotic administration and development of an animal model based design of rapid predictive test for metabolic dysfunctions due to drug administration *in order to evaluate the impact of antipsychotic drugs in the CNS and its regulation of metabolic function through the hypothalamic-periphery axis. Two different animal models of schizophrenia will be used: the transgenic mouse model of DN (dominant negative) human DISC1 (Disrupted-in-schizophrenia 1) and the neurodevelopmental rat model of neurogenesis disruption with prenatal administration of the cytostatic agent methylazoxymethanol.*

The ESR will analyze how the antipsychotic drug treatment alters metabolic regulators in the CNS that will have an effect on neural activity and impact the neurodegenerative profile of the schizophrenic mice. We also expect to find differences in the metabolic drug response profile in the CNS of schizophrenic mice relative to controls, whose potential value as biomarkers will be validated in the human part of the study for tool development.

Host: Bn'ML Behavioral & Molecular Lab (Braga, Portugal), (company).
Supervisors: Professor Joao Bessa and Dr. Eugenia Carvalho (For information on the company see http://www.bnml.eu/ and contact joaobessa@med.uminho.pt)

ESR15 will perform cell data integrative analysis, biomarker validation and tool development. *The ESR will carry out an integrative omic analisis of cellular stress responses to antipsychotic treatment, following validation of identified protein biomarkers, implementation of methodological standarization protocols and tool development based on protein analysis.*

The ESR will use cellomics data from drug stressed cells and human blood samples to identify protein biomarkers of drug induced metabolic stress and the analysis of the biomarkers will be validated by the ESR on independent samples. The ESR will also work on the standarization of the analysis protocols and will develop a prototype diagnostic tool and test its applicability to other drug induced metabolic effects.

Host: Cell Stress Discoveries (Galway, Ireland), (company).
Supervisors: Professor Afshin Samali and Professor Boaz Tirosh (For information on the company see https://cellstressdiscoveries.com/ and for detail of the project please contact afshin.samali@nuigalway.ie or eugeniamlcarvalho@gmail.com).