



HR EXCELLENCE IN RESEARCH

14 PhD positions available in the Marie Skłodowska Curie Innovative Training Network "TRAIN-ERS" (H2020-MSCA-ETN - 675448)

located in Ireland, France, UK, Belgium, Sweden, Germany, Israel and Austria which focuses on investigating the Endoplasmic Reticulum Stress Response in Health and Disease.

Project background and goal: *Endoplasmic reticulum (ER)* stress is now emerging as a common feature in the pathology of numerous diseases including cancer, neurodegenerative disorders, metabolic syndromes and inflammatory diseases, annually affecting millions of patients worldwide, and posing an enormous cost burden on the health sector. ER stress is caused by impaired function of the ER and accumulation of unfolded proteins in this compartment which triggers a set of signalling pathways termed the *unfolded protein response (UPR)*. The UPR is an adaptive response that aims to resolve the stress through a multi-pronged approach, however, when ER stress cannot be resolved, the UPR induces cell death. The molecular mechanisms involved in transition of the UPR from a protective to a death response are incompletely understood, but are fundamental to developing strategies to limit or avoid the pathological consequences of ER stress. Therefore understanding the ER stress response has the potential to allow us to tackle many ER stress-associated diseases and it thus represents a potential therapeutic intervention point that can be exploited to develop novel therapies and new diagnostic and prognostic markers for a wide range of diseases. This programme will bring young researchers together with world-leading academics, clinicians and industry personnel, who will form a network of excellence aimed at understanding the ER stress response and applying this understanding to provide knowledge-driven strategies for the treatment of ER stress-associated 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).

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 TRAIN-ERS APPLICATION FORM. This form should be completed and emailed to trainers@nuigalway.ie by 5.00pm on 15th Nov 2015. 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-November to mid-December. Applicants will be informed of the outcome by end of December 2015 (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 1st April 2016.

PhD Projects

ESR1: Omics technologies to understand the ER stress response

Studies in ER stress to date have largely used traditional single gene and protein centred approaches in diverse disease models, and there has been no comprehensive study to understand the global response to ER stress in normal cells. **ESR1** will use cutting edge “omic” technologies to comprehensively detect the global cellular changes in RNA, Protein, glycosylation and metabolites due to ER stress in normal epithelial cell lines.

Host: National University of Ireland, Galway – NUIG (Galway, Ireland)

Supervisor: Dr Adrienne Gorman and Prof. Afshin Samali (For information on this lab and more detail of the project please see www.apoptosis.ie and <http://www.nuigalway.ie/about-us/jobs> or contact afshin.samali@nuigalway.ie or adrienne.gorman@nuigalway.ie)

ESR2: Contribution of RIDD activity to cell survival/death

To uncover key RIDD substrates that influence cell survival and cell death **ESR2** will use recombinant IRE1 α cytosolic domain and shRNA technology to assess the contribution of RIDD substrates to normal cellular processes and on cancer cell characteristics (e.g., chemoresistance and cell growth, adhesion/migration and invasion

Host: Institut national de la santé et de la recherche médicale - INSERM (Rennes, France)

Supervisor: Dr Eric Chevet (For information on this lab and more detail of the project please see <http://oss-clcc-rennes.com/> or contact eric.chevet@inserm.fr)

ESR3: ER stress regulated autophagy and autophagic cell death

Autophagosome may function as a platform facilitating pro-caspase-8 activation and thereby influencing cell fate. **ESR3** will use a proteomics approach to investigate the full components of the caspase-8 activating complex, including the inhibitors and regulators of the complex. Genetic approaches (overexpression, siRNA, Crispr/CAS9) will be used to test the effect of different components of caspase-8 activating complex on autophagy and cell fate.

Host: Bellvitge Biomedical Research Institute - IDIBELL (Barcelona, Spain)

Supervisor: Dr Cristina Muñoz Pinedo (For information on this lab and more detail of the project please see <http://www.idibell.cat/modul/cell-death-regulation/en> or contact cmunoz@idibell.cat).

ESR4: Deciphering and exploiting aggresome-associated cell death initiation to predict anti-cancer treatment efficacy.

ESR4 will investigate the kinetics and quantities of apoptosis vs. necroptosis activation using semi-HTS flow cytometry and biochemistry in melanoma models. Highly sensitive FRET-based time-lapse imaging of caspase activation in combination with biophotonic indicators for necroptotic membrane permeabilisation will provide insight into whether both cell death modes can be co-activated at the single cell level. Components of systems biological network analysis will be employed for data interpretation and additional mechanistic insight, leading towards the development of predictive treatment response models.

Host: Royal College of Surgeons Ireland - RCSI (Dublin, Ireland); note that the group will move to University Stuttgart (Germany)

Supervisor: Dr Markus Rehm (For information on this lab and more detail of the project please see <http://pi.rcsi.ie/pi/mrehm/> or contact mrehm@rcsi.ie)

ESR5: Functional role of the newly discovered PERK-interacting partners

Understanding the functional impact of the PERK-interactome and its dynamic changes during ER stress will be crucial to understand the global role of PERK in disease conditions (e.g., cancer) and to develop strategies aimed at blocking specific interactions, while sparing others. The host laboratory has identified new molecular partners of PERK, which modulate the dynamic of interorganellar contact sites and response to Ca²⁺ fluxes, independent of the UPR. **ESR5** will investigate how specific perturbations/disruptions of the newly identified PERK-interactome (shRNA, CRisp-CAS9, pharmacological inhibition) affect key cancer cell features under basal or ER stress conditions.

Host: KUL (Leuven, Belgium)

Supervisor: Prof. Patrizia Agostinis (For information on the Cell Death Therapy and Research lab (CDRT) and more detail of the project please see <https://gbiomed.kuleuven.be/english/research/50000618/index.html> or contact Patricia.Agostinis@med.kuleuven.be)

ESR6: UPR as a novel therapeutic target in paediatric cancers

This project will focus on exploring the potential of targeting the UPR in paediatric cancers. **ESR6** will screen a large number paediatric cancer cell lines and primary patient material for sensitivity to ER stress inducers to identify childhood cancers that are particularly prone to ER stress. Combinations of ER stress inducers and other cytotoxic drugs will be tested to identify synergistic drug interactions and a synthetic lethality screening assay using a genome-wide shRNA library will be used to discover novel candidate genes that regulate ER stress-triggered cell death in childhood cancers. Candidate genes will be characterized and validated in cell culture and *in vivo* using the chorioallantois membrane model.

Host: Goethe University Hospital Frankfurt - GUF (Frankfort, Germany)

Supervisor: Prof. Simone Fulda (For information on this lab and more detail of the project please see <http://www.kinderkrebsstiftung-frankfurt.de/index.php/forschen/institut-fuer-experimentelle-tumorforschung-in-der-paediatric> or contact Simone.Fulda@kgu.de)

ESR7: Assessing the potential of IRE1/XBP1s for therapeutics and diagnostics in breast cancer (BC)

ESR7 will determine whether the IRE1 α /XBP1s signalling axis can serve as a viable diagnostic or prognostic marker or therapeutic target in BC, by analysing XBP1s expression in approximately 100 BC and normal matched patient tissue samples. ESR7 will also examine the therapeutic potential of blocking IRE1 α /XBP1s signalling in a panel of human BC cell lines (T47D, SKBR3, MDA-MB231, SKBR3, BT474) and the non-tumorigenic breast cell line MCF10A.

Host: National University of Ireland, Galway – NUIG (Galway, Ireland)

Supervisor: Dr Adrienne Gorman & Prof. Afshin Samali (For information on this lab see www.apoptosis.ire and more detail of the project please see <http://www.nuigalway.ie/about-us/jobs/> or contact afshin.samali@nuigalway.ie or adrienne.gorman@nuigalway.ie).

ESR8: ER stress in neurodegenerative disease

Protein misfolding is a common feature of several neurodegenerative diseases which leads to a profound upregulation of ER stress markers. **ESR8** will determine whether the IRE1 α /XBP1 signalling component of UPR is a viable target for treatment of amyotrophic lateral sclerosis/ motor neuron disease (ALS), in view of the involvement of this pathway in ALS and the finding that a mutation in the familial form of ALS attenuates this pathway. This hypothesis will be tested by analysing the therapeutic potential of IRE1 activating peptides and peptide mimetics in a range of ALS models including cell lines harbouring mutations associated with familial ALS and a motor neuron cell line, NSC-34, to assess their effects on formation of ubiquitinated protein aggregates, autophagy and motor neuron survival

Host: Imperial College London - ICL (London, UK)

Supervisor: Prof. Jackie de Belleruche (For information on this lab and more detail of the project please see <http://www.imperial.ac.uk/people/j.belleruche> or contact j.belleruche@imperial.ac.uk)

ESR9: ER stress and UPR in inflammatory liver disease and shock

ESR9 will identify specific inflammatory mediator patterns inducing ER stress and will clarify the impact of ER stress/UPR on the development of liver dysfunction upon shock and inflammation using *in vitro* models and *in vivo* models of shock (hemorrhagic shock and local ischemia) and inflammation (bacterial endotoxin induced systemic inflammation). The main objective of this study will be to understand the impact of ER-stress/UPR on organ/cellular function and inflammatory response in these experimental models. These data will provide a rationale for the development of novel diagnostic and therapeutic strategies focused on modulation of UPR.

Host: Ludwig Boltzmann Society - LBG (Vienna, Austria)

Supervisor: Dr Andrey Kozlov (For information on this lab and more detail of the project please see <http://trauma.lbg.ac.at> or contact andrey.kozlov@trauma.lbg.ac.at)

ESR10: Development of inhibitors to block essential protein-protein interactions

ESR10 will use a range of *in silico* software for homology modeling, protein-protein interaction studies, and virtual high-throughput screening in order to develop small molecule and peptidomimetic inhibitors targeting RtcB-XBP1-mRNA interaction, IRE1 activity and interactions, and ATF6. Part of the work is done in close collaboration with ESR11 and 12, and also involves experimental work (secondments) at participating laboratories to verify mechanisms of action of said compounds.

Host: Gothenburg University - UGOT (Gothenburg, Sweden)

Supervisor: Prof. Leif A. Eriksson (For information on this lab and more detail of the project please see http://cmb.gu.se/english/about_us/staff?languageId=100001&userId=xeleif or contact leif.eriksson@chem.gu.se)

N.B. To apply for this position you need to send in a central application as outlined in the application procedure above but in addition applicants need to apply directly at http://www.gu.se/english/about_the_university/announcements-in-the-job-application-portal/?languageId=0&disableRedirect=true&id=19144&Dnr=724246&Type=E

ESR11: Developing IRE1-activating agents for the treatment of degenerative diseases

ESR11 will combine and analyse all the data available on the peptide activators of IRE1 and the binding site interactions of IRE1 activators (Hsp72, Bim, PUMA) to model the interactions and to screen virtual compound libraries for hits that mimic the effects of the activator peptides or proteins. These IRE1-activating compounds will be synthesised and tested in *in vitro* and in cell based assays for effects on cellular processes, on signalling networks, on survival under ER stress conditions and on the secretome.

Host: Institut national de la santé et de la recherche médicale - INSERM (Rennes, France)

Supervisor: Dr Eric Chevet (For information on this lab and more detail of the project please see <http://oss-clcc-rennes.com/> or contact eric.chevet@inserm.fr)

ESR12: Targeting ATF6 as an anti-cancer strategy

ESR12 will develop strategies to block ATF6 activation by targeting its processing at the Golgi. **ESR12** will carry out a virtual screen for compounds that inhibit ATF6 processing and develop a GFP-tagged ATF6 cell-based assay in order to test and prioritize hit compounds from the virtual screen. ATF6 inhibitors will be tested for efficacy in breast cancer models to determine if targeting this branch of the UPR is a viable therapeutic strategy.

Host: National University of Ireland, Galway – NUIG (Galway, Ireland)

Supervisor: Dr Adrienne Gorman & Prof. Afshin Samali (For information on this lab see www.apoptosis.ie and more detail of the project please see <http://www.nuigalway.ie/about-us/jobs/> contact afshin.samali@nuigalway.ie or adrienne.gorman@nuigalway.ie)

ESR13: Development of a multiplexed serum test based on ER stress biomarkers

ESR13 will develop a biochip that can be used to detect pathological levels of ER stress markers in serum. **ESR13** will assess novel candidate markers of ER-related stress identified in hepatic, motor neuron and leukemia cells with/without ER stress-inducing agents and identify common ER stress-related secreted factors and cell type specific ER stress related secreted factors. Based on this data **ESR13** will develop biochips that can detect ER stress-related secreted factors in well-defined clinical sample cohorts to investigate their potential for disease state identification.

Host: Randox Teoranta (Donegal, Ireland) (company)

Supervisor: Dr Ciaran Richardson & Prof Afshin Samali (further information on the company See <http://www.randox.com> or contact Ciaran.Richardson@randox.com)

ESR14: Assessing the UPR for predictive value in melanoma patients

ESR14 will deep sequence and quantitate ER stress-related factors in tumour tissue samples taken from a cohort of 100 melanoma patients who were treated with Pembrolizumab (Keytruda) or Ipilimumab (Yervoy). Subsequently, **ESR14** will use the OPTI high level multiscale modelling platform to determine the value of these markers for predicting response to immunotherapy prior to treatment.

Host: Optimata - OPTI (Bene-Atarot, Israel) (company)

Supervisor: Prof Zvia Agur & Prof Afshin Samali (For information on this lab and more detail of the project please see www.optimata.com or contact agurz@optimata.com)