# TRIM-NET
## a training network in drug discovery targeting TRIM ubiquitin ligases is recruiting
# 12 PhD students

Marie Skłodowska-Curie Action - Innovative Training Networks (ITN)
GA 813599 – H2020-MSCA-ITN-2018

## General description of the Network

The Tripartite motif (TRIM) family of Ubiquitin E3 ligases plays an important role in many physiological processes and in many diseases including cancer, neurodegenerative and neuro-muscular disorders and rare genetic diseases. As such, they are excellent targets for therapeutic manipulation. TRIM-NET is a training programme for Early-Stage Researchers to identify novel therapeutic targets and to develop the strategies to validate them in preclinical studies. The TRIM-NET network will integrate complementary expertise and multidisciplinary approaches to exploit common targeting strategies for translational applications. The consortium will train a cohort of young researchers in skills and expertise essential for biomedical research focusing on: i) determining how TRIM proteins contribute to disease; ii) developing strategies to modulate TRIM protein activity; iii) designing high throughput screening assays for drug discovery. The project consists of 12 individual research projects (see below the list of available research projects and host laboratories). As the scientific work packages are highly integrated, recruited students will avail of techniques and training opportunities, including secondments, across the work packages. Through a unique international partnership between academic and non-academic partners the TRIM-NET training programme will provide young researchers with skills required for biomedical research in industry and academia.

## Eligibility and Requirements

- Not having a doctoral degree yet
- Less than 4 years full-time research experience
- A degree which entitles to embark on a doctorate in the host countries
- Less than 12 months spent in the host country in the 3 years prior to the recruitment
- A strong background in Biology, Biochemistry, Chemistry, Medicine or related fields according to the individual research projects
- The relevant PhD accession title should be achieved by June 2019 through September 2019 according to the specific PhD programmes and countries

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## Job offer and Benefits

- Attractive salary
- 3-year full-time employment contract in accordance with the Marie Skłodowska-Curie Action regulations for Early Stage Researchers;
- Enrollment in a PhD programme at the local partner's institution. In case the student is enrolled in a doctoral programme in a country where the duration of the PhD study is beyond the 3-year-MSCA contract, additional funding for the additional year(s) will be provided by the host group
- Access to state-of-the-art research and supervision by recognized experts
- Participation in network-wide training activities, schools and conferences
- Secondments periods at other network partners' labs.

## Application procedure

Applications in English should include:

- A cover letter indicating the top three projects of election in the order of preference (see below) and the indication of the countries of residence during the last 3 years;
- CV (contact details, education, work experience, list of publications, prizes/awards, language skills, etc….);
- A motivation letter;
- A digital copy of the degree certificate and official academic transcripts of Bsc and Msc studies (Master diploma/certificate or equivalent qualification giving access to the Doctoral Programme **+** Transcript of Records including examinations and scores obtained. If the documents are issued in a language other than English, a translation must be included, along with the original document);
- A documentation of English language qualifications;
- Two recommendation letters sent directly by the referees to *trimnet@units.it* with the subject: "Letter concerning - Surname Name" and full contact details of the reference persons;

Application in a single pdf file should be sent by e-mail to *trimnet@units.it* with indication of "TRIM-NET application" in the subject line. Equal consideration will be given to female and male applicants.

## Deadlines of Application, Evaluation process and Starting date

- Deadline for Application: **April 15, 2019**.
- The merit-based recruitment process will be on a competitive basis across all applicants for each project.
- Short-listed students will be interviewed via Skype on **May 9-10, 2019**.
- Students are expected to initiate their contracts between June 1$^{st}$, 2019 and November 1$^{st}$, 2019 depending on the PhD enrollment rules of the different countries.

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## Overview of the 12 vacant ESR positions

| | TITLE | OBJECTIVEs | HOST |
|---|---|---|---|
| **ESR1** | *Regulation of α-synuclein expression by TRIM17 and TRIM41 in Parkinson's Disease* | TRIM17 increases α-synuclein expression by inhibiting ubiquitination/degradation of the transcription factor ZSCAN21 mediated by TRIM41. The aim is to assess 1) the role of this pathway in Parkinson's disease models; 2) the impact of TRIM41 and ZSCAN21 mutations identified in patients; 3) the molecular mechanisms of TRIM41 inhibition by TRIM17. | *Solange Desagher* CNRS-IGMM, Montpellier, France (www.igmm.cnrs.fr/en/team/mecanismes-moleculaires-de-regulation-de-lapoptose) |
| **ESR2** | *Autophagic defects in Lafora disease due to mutations in the TRIM-like E3 ligase Malin* | Lafora progressive myoclonus epilepsy is caused by mutations in the TRIM-like E3-ubiquitin ligase malin. This study will identify the role of malin in pathophysiology. Interactomics and proteomic techniques will be used to identify substrates of malin. We will also pay attention to the deubiquitinases that accompany malin in its action. | *Pascual Sanz* CSIC, Valencia, Spain (http://www3.ibv.csic.es/ibv03/USN/usn-gente.php?lang=uk) |
| **ESR3** | *Function of TRIM32, the ubiquitin ligase mutated in Limb Girdle Muscular Dystrophy 2H* | TRIM32 is the gene responsible for Limb Girdle Muscular Dystrophy type 2H and Sarcotubular Myopathy. The objective of this project is to thoroughly define TRIM32 ubiquitin E3 ligase activity by assessing the specific TRIM32-E2 complexes and the ubiquitin chains formed for the control of specific muscular targets, combining biochemical, biophysical and cell biology approaches. | *Germana Meroni* DSV, University of Trieste, Trieste, Italy (dsv.units.it/en/research/researchareas/biomedicine?q=en/node/20434) |
| **ESR4** | *Developing new strategies to limit TRIM63/MuRF1-mediated muscle protein loss* | TRIM63/MuRF1 targets muscle contractile proteins during many diseases (cancer, etc.) in combination with E2 enzymes, and is associated with patient's health degradation. This study aims at characterizing functionally (in vivo transfection, immunohistochemistry) and biochemically TRIM63-E2 couples. Pharmacological drugs will be designed to inhibit TRIM63-E2s interaction to fight against patient's weakness. | *Daniel Taillandier* INRA, Clermont Ferrand, France (https://www6.ara.inra.fr/unh_eng/Teams/PROSTEOSTASIS/Staff/Dr.-Daniel-Taillandier) |
| **ESR5** | *Determining the role of TRIM25 in Androgen Receptor-dependent Cancers* | Prostate cancer is one of the leading cancer deaths for men. By applying state-of-the-art techniques in molecular biology and biochemistry, we will investigate how TRIM25 controls androgen receptor activity and proliferation and migration of prostate cancer cells and elucidate its suitability as a target for drug development. | *Christine Blattner* KIT, Karlsruhe, Germany (www.itg.kit.edu/blattner.php) |
| **ESR6** | *Defining the role of TRIM33 in hormone-dependent breast cancer* | Around 75% of all breast cancers are positive for the Estrogen Receptor (ER), which is considered the main driver of the disease. In a siRNA screen targeting all 781 E1, E2 and E3 ligases throughout the human genome, we set out to discover novel regulators of ER stability. We identified TRIM33 as a crucial factor to regulate ER levels and activity. We aim to unravel the biological interplay between ER function and TRIM33, and explore how this interaction can be therapeutically exploited using novel inhibitors. | *Wilbert Zwart*, NKI-AVL, Amsterdam, The Nederlands (nki.nl/divisions/oncogenomics/zwart-w-group) |
| **ESR7** | *Determining the role TRIM28 in hormone-dependent prostate cancer* | We previously identified TRIM28 as a direct interactor of the Androgen Receptor in prostate cancer cells, critically involved in prostate cancer cell proliferation. This study will: 1. identify the functional contribution of TRIM28 on Androgen Receptor function in prostate cancer cells, 2. Unravel the underlying basis of the observed genomic selectivity, 3. Reveal the clinical implications of TRIM28 on prostate cancer patient outcome and response to therapy, and 4. Expose how this TRIM28/AR interaction could be therapeutically exploited in the treatment of prostate cancer patients. | *Wilbert Zwart*, NKI-AVL, Amsterdam, The Nederland (nki.nl/divisions/oncogenomics/zwart-w-group) |

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| **ESR8** | *Dissecting TRIM8 function in the pathogenesis of glioblastoma* | Reduced E3 ubiquitin ligase activity of TRIM8 contributes to the glioma pathogenesis.<br>This study aims to identify TRIM8-partners and TRIM8 glioma-related functions. Transcriptomic, proteomic, and bioinformatics will be exploited to identify TRIM8-related glioma signatures, identify novel pathways that correlate with the pathophysiology of this tumour, and ultimately indicate therapeutic avenues | *Giuseppe Merla*, CSS-IRCCS, San Giovanni Rotondo, Italy (https://www.operapadrepio.it/it/genetica-medica/personale/2720-merla-giuseppe.html) |
| **ESR9** | *Understanding the role of Arsenic in modulating PML/TRIM19 activity* | Arsenic is used therapeutically to treat Acute Promyelocytic Leukaemia by inducing SUMO-dependent, ubiquitin-mediated degradation of the PML-RAR oncoprotein. The objective of the work will be to define the mechanism by which arsenic induces SUMO modification of PML (TRIM19) and will involve a combination of biochemical, proteomic and structural biology approaches. | *Ronald T. Hay*, University of Dundee, Dundee, UK (www.lifesci.dundee.ac.uk/groups/ron_hay) |
| **ESR10** | *Study of the TRIM-E2 interaction specific determinants and identification of TRIM-associated DUBs* | The first objective of this project is to understand E3-E2 pair selection and its determinants for the TRIM proteins studied within this network (TRIM8, 17, 19, 25, 28, 32, 33, 41, 63 and Malin) with the ultimate goal of exploring novel strategies of drug design and screening to interfere with specific E3 activities. As a further objective, mid-throughput screening assays will be employed to identify the DUBs implicated in the TRIM-associated disease pathways under study within the consortium. | *Germana Meroni*<br>DSV, University of Trieste, Trieste, Italy (dsv.units.it/en/research/researchareas/biomedicine?q=en/node/20434) |
| **ESR11** | *Development of TRIM-specific assays suitable for High-Throughput-Screening* | We will develop TRIM assays that will be used in high throughput small molecule screening campaigns to develop TRIM inhibitors in collaboration with ESR12. Prior experience with protein expression and purification/ structural biology is desired. | *Huib Ovaa*, LUMC, Leiden, The Nederlands (http://www.ovaalab.nl/index.html) |
| **ESR12** | *Design of small compounds to modulate TRIM-substrate interactions* | Medicinal chemistry will be used to develop screening hits into specific TRIM inhibitors that will be further validated in collaboration with TRIM-NET labs. We look for a candidate with a background in organic synthesis/ medicinal chemistry. | *Huib Ovaa*, LUMC, Leiden, The Nederlands (http://www.ovaalab.nl/index.html) |

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