PIPGEN

INTERNATIONAL PHD FELLOWSHIP RECRUITMENT CALL

PIPgen - PI3K/PTEN-related monogenic disease to understand cancer

15 full-time Early Stage Researcher Positions

HOST INSTITUTIONS:

- **Josep Carreras Leukaemia Research Institute,** Badalona, Spain
- **University College of London**, London, UK
- **Université de Paris**, Paris, France
- **Erasmus MC**, Rotterdam, Netherlands
- **Institut national de la santé et de la recherche / Université de Toulouse III,** Toulouse, France
- **Amsterdam University Medical Centres (UMC),** Amsterdam, Netherlands
- **Cambridge University**, Cambridge, UK
- **Radboud universiy medical centre,** Nijmegen, Netherlands
- **CIC bioGUNE**, Bilbao, Spain
- **Kither Biotech**, Torino, Italy
- **qGenomics**, Esplugues del Llobregat, Spain

RESEARCH PROFILE: First Stage Researcher (R1[1])

APPLICATION DEADLINE: 4th July 2021

EU RESEARCH FRAMEWORK PROGRAME: HORIZON 2020

MARIE SKOLODOWSKA CURIE GRANT AGREEMENT NUMBER: 955534

[1] First Stage Researcher (R1) PhD candidate or equivalent. Early stage researcher with less than 4 years FTE research experience.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 955534

TIMELINE:

OFFER DESCRIPTION:

The Innovative Training Network (ITN) **"PIPgen - PI3K/PTEN-related monogenic disease to understand cancer"** is recruiting 15 highly motivated PhD candidates through an international transparent and open recruitment procedure. The fellowships are funded by the European Commission's Horizon 2020 programme under the ITN-Marie Skłodowska-Curie grant agreement Nº 955534

More info at: https://ec.europa.eu/research/mariecurieactions/actions/research-networks_en

ABOUT THE PIPgen NETWORK

The **PIPgen** network brings together 9 leading European basic and clinical institutions and 3 private companies experts in the PI3K/PTEN- related diseases, to train 15 researchers in a wide range of scientific and complementary competences. Selected candidates will carry out specific projects under the supervision of a Principal Investigator within one of the 11 world-leading European host institutions from the network. They will also perform secondments in other European institutions within the network to provide the needed interactions to achieve research and training excellence, and to improve their future career perspectives.

Fellows will be enrolled in a PhD programme and will receive an outstanding and tailored training designed specifically for them. The embedding within the PIPgen network, with experienced trainers from academia and industry and from two research environments (clinical and basic), offers a unique multidisciplinary and multisectoral training opportunity in the field of PI3K/PTEN-related diseases.

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SCIENTIFIC PROJECTS

PIPgen stems from the emerging links between monogenic rare diseases and cancer, and how these fields can cross-fertilise and inform an integrated approach to both their understanding and treatment. Monogenic diseases offer 'clean' molecular, cellular and organismal information about the affected genes, whereas cancer is a compendium of genetic and epigenetic perturbations illustrative of complex diseases. Genetic alterations in the phosphoinositide 3-kinase (**PI3K)/PTEN pathway** are a common event in both monogenic rare diseases and in cancer, presenting a truly unique paradigm of which PIPgen will take advantage. PIPgen aims to critically contribute by providing a dynamic learning strategy to enhance our understanding of the PI3K/PTEN pathway based on the molecular, biological and clinical integration of both pathological scenarios. **PIPgen has been conceived with the view to make a real clinical and therapeutic impact without losing focus on the underpinning basic bioscience**.

PhD POSITIONS

PhD Project 1: Mechanism of action of PIK3CA mutation in cancer and overgrowth

Activating *PIK3CA* mutations lead to cancer and the *PIK3CA*-related overgrowth spectrum (PROS). Despite years of investigation, many questions remain about *PIK3CA* biology, signalling and pathway regulation. The aim of this project is to understand context-dependent and *PIK3CA*-mutant-specific biology, and how to therapeutically interfere with this pathway, both in cancer and PROS. We have made several interesting novel observations on *PIK3CA* biology and signalling that will be explored in this project, using advanced genetic and pharmacological PI3K approaches. Drug interventions will be tested in *in vitro* and *in vivo* studies.

Host: University College of London (UCL), UK

Supervisor: Prof Bart Vanhaesebroeck

Doctoral programme: University College of London

Envisioned secondments: Josep Carreras Institute , qGenomics

To apply for the UCL positions, in addition to the procedures outlined here, a further application will need to be completed via the UCL website – this is to conform with UCL's own recruitment process. This second step is not yet available online, but we will inform candidates as soon as it opens.

PhD Project 2: Understanding the physiopathology of PROS

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A challenging issue is the broad clinical presentation of PROS patients. To favour the inclusion of patients in potential clinical trials, stratification is mandatory. Based on our clinical expertise, we intend to classify patients according to the tissue layers that are involved in the malformation. To better understand the different subgroup of patient phenotypes, we have generated mouse models expressing oncogenic PIK3CA in specific tissues (including adipose, osteoblast, lymphatic, endothelial cells, muscle, Schwann cells). With a specific focus on veins and lymphatic vessels, ESR2 will express PIK3CAmut in genetically modified mouse models, followed by characterising their macroscopy phenotype, scRNAseq, and culture of lesion-derived cells.

Host: Université de Paris, France.

Supervisor: Prof Guillaume Canaud

Doctoral programme: Université de Paris

Envisioned secondments: KITHER, UCL

The selected candidate will have to undergo a second row of application in order to formally be admitted and allowed to enrol in the Université de Paris.

PhD Project 3: Improving recognition of patients with PHTS phenotypes by easy-to-apply sets of clinical criteria

PTEN Hamartoma Tumour Syndrome (PHTS) is a rare genetic predisposition that results in a broad spectrum of diseases. Most of these disesase are on their own common in the general population which hampers recognition of these rare PHTS patients. In addtion, each disease expression of PHTS is diagnosed by different health care disciplines and at different ages, such as skin lesions (dermatologist), vascular malformation (radiologist), developmental delay (neurology), an enlarged thyroid (endocrinologist) or breast cancer (oncologist/surgeon). We will determine easy-to-apply sets of clinical criteria that can be assessed by each healthcare provider who diagnoses a common feature of PHTS. In a large cohort of PHTS patients and PTEN-negative control patients extended clinical characteristics will be collected and assessed. The best performing clinical criteria will be assessed for futher implementation.

Host: Radboud university medical centre, NL.

Supervisor: Prof. Dr. Nicoline Hoogerbrugge and Dr. Janet Vos

Doctoral programme: Radboud University Nijmegen The Netherlands

Envisioned secondments: Gqenomics, cic-BIOgune

Position requirements: epidemiological and (bio)medical background, and understanding written Dutch is required.

PhD Project 4: Understanding vascular malformations in PHTS

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 955534

30% of the patients with PHTS suffer from vascular malformations. Yet, this clinical condition has been under investigated in PHTS patients. ESR4 will: establish endothelial and epithelial cell models of the disease by introducing PTEN mutations and characterise their functional effects, cellular phenotyes and genetic instability. Primary endothelial cells derived from PHTS patients will be isolated, an in vivo model of the disease using a transgenic mouse model will be generated, combining a germline heterozygous background with a second PTEN hit under the control of a vascular-specific promoter, and the models will be screened for corrective treatments in FDA-approved drug screen**.** Biology and preclinical insight of these PHTS-derived vascular malformations models will be cross-compared with PHTS-derived epithelial tumours.

Host: Institut de Recerca contra la Leucèmia Josep Carreras (Josep Carreras Institute), Spain.

Supervisor: Dr. Sandra Castillo

Doctoral programme: University of Barcelona

Envisioned secondments: Radboudumc, U-Paris.

PhD Project 5: Biomarkers of chronically hyperactivated PI3Kδ in patients with APDS

Activated PI3 kinase Delta Syndrome (APDS) is a rare disease previously discovered by the group of Prof Sergey Nejentsev (Angulo et al, Science, 2013). It is caused by mutations that increase PI3 kinase δ activity. APDS patients are immunodeficient and have high risks of bronchiectasis, autoimmune manifestations and lymphomas, suggesting that hyperactivated PI3 kinase δ contributes to the pathogenesis of these disorders. ESR5 will use advanced cell and molecular techniques to characterise immunological consequences of chronically hyperactivated PI3 kinase δ in APDS as well as related common disorders.

Host: Amstersdam UMC (location VUmc), NL.

Supervisor: Prof Sergey Nejentsev

Doctoral programme: Vrije University of Amsterdam (4 Years PhD Program)

Envisioned secondments: University of Cambridge, Inserm

PhD Project 6: Studying T cell exhaustion in a model of APDS

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 955534

Patients with APDS experience T cell exhaustion in response to chronic activation by herpes family viruses. Similarly, mice with an activated PI3Kd mutation raise highly effective immune responses to acute viral infections, but preliminary data show they fail to control chronic infections effectively. We will generate proteomic data sets of T cells obtained from infected mice and map PI3Kd-dependent changes. Candidate genes responsible for T cell exhaustion in a PI3Kd-dependent manner will be CRISPR out to determine the mechanisms of T cell exhaustion. Pharmacological strategies to reverse T cell exhaustion will be explored.

Host: University of Cambridge (UCAM), UK

Supervisor: Klaus Okkenhaug

Doctoral programme: University of Cambridge

Envisioned secondments: Amstersdam UMC, KITHER

PhD Project 7: Role of PTEN/PI3K mutations in increased risk for autism spectrum disorder (ASD)

Mutations in the PTEN and PI3K genes have been described to increase the risks for ASD. However, the function of these proteins in the brain and their role in ASD are largely unknown. ESR7 will: characterize the interactions between PTEN and PI3K mutations and the mTOR pathway in neurons at the molecular and cell morphological level; perform behavioural phenotyping of transgenic mouse models of PTEN and PI3K mutations found in the patient cohorts behavioural and cognitive tests in patient cohorts; use functional ultrasound to investigate brain-wide activity in one of the mouse models

Host: Erasmus University Medical Center Rottedam (ErasmusMC), NL.

Supervisor: Dr. Aleksandra Badura

Doctoral programme: Erasmus University (4 years PhD Programme)

Envisioned secondments: UCAM, UCL

PhD Project 8: The role of PI3Kdelta in solid tumours and its modulation using novel pharmacological tools

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 955534

There is emerging evidence for a cancer-cell-intrinsic role of PI3Kdelta in solid tumours, but this has not been formally proven. ESR8 will investigate the role and mechanism of action of cancer-cell-intrinsic PI3Kdelta in solid tumours, and its importance in responsiveness to novel pharmacological tools that modulate PI3Kdelta activity (such as IOA-244 from iOnctura and others). The focus will be on cell types expressing high levels of PI3Kdelta, including glioblastoma and melanoma, with some studies on specific lymphoma subtypes. ESR8 will perform CRISPR-out the PI3Kdelta gene from selected tumour cell lines to investigate the impact in cancer-relevant biology *in vitro* and *in vivo*, using advanced signalling studies by proteomic and genomic analyses (such as RNAseq, epigenetics) and cell biology.

Host: University College of London, UK.

Supervisor: Prof Bart Vanhaesebroeck

Doctoral programme: University College of London

Envisioned secondments: iOnctura, UCAM

To apply for the UCL positions, in addition to the procedures outlined here, a further application will need to be completed via the UCL website – this is to conform with UCL's own recruitment process. This second step is not yet available online, but we will inform candidates as soon as it opens.

PhD Project 9: Mechanical stress & signal integration by PI3Ks for the control of tumour growth

Approaching mechanical properties of tumours appear as a novel means to treat cancer. PI3K signalling is increased in more than 50% of cancer patients, how PI3K integrates mechanical signal and whether its inhibition could have an impact on the efficiency of these novel strategies is unknown. ESR9 will: establish an in vitro patient or murine organoid model that mimic mechanical stress (compression, tension, shear) and genetic heterogeneity found in pancreatic cancer, map how PI3K activity influences response to mechanical stress in various genetic environments and determine the mechanosensitive determinants that prevent cell growth & migration, validate the most efficient approach in preclinical settings.

Host: Institut national de la santé et de la recherche / Université de Toulouse III (INSERM), France

Supervisors: Dr. Julie Guillermet-Guibert

Doctoral programme: Université Toulouse III – Paul Sabatier

Envisioned secondments: Josep Carreras Institute, U-Paris

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 955534

PhD Project 10: (poly)Genic alterations which emerge from monogenic PTEN-loss driven prostate cancer

Prostate tumours are associated to the process of aging and lifestyle, which could relate to the progressive accumulation of mutations or to the decline of systemic antitumoral capacity. ESR10 will characterise in a PTEN loss-driven mouse model, the impact of aging and lifestyle factors in the susceptibility to develop prostate lesions and we will combine this information with data derived from human prostate cancer specimens. We will perform molecular characterisation of the tumour and stromal component, seeking to define key drivers of the tumorigenic process that can be mechanistically deconstructed. We will capitalize on human prostate cancer multi-omics datasets to determine the clinical relevance of the drivers derived from the mouse model. It is intended that ESR10 will have a predominant training in computational biology, complemented with cellular and molecular biology (gene editing technologies that enable us to alter the prostate genetic makeup based on the findings derived from monogenic disease that will be produced in PIPgen). This project has the impact to provide new research tools to the field while generating key knowledge that can be critical for prostate cancer management.

Host: CIC bioGUNE (cic-BIO), Spain

Supervisors: Dr. Arkaitz Carracedo and Isabel Mendizabal

Doctoral programme: Universidad País Vasco

Envisioned secondments: qGenomics, Inserm

PhD Project 11: Understanding the role of activated PI3Kδ mutations in B cell lymphoma

Patients with APDS are at increased risk of developing B cell lymphoma. ESR11 will characterise a novel mouse model of B cell lymphoma driven by activated PI3Kδ and BCL6. The student will determine the sensitivity of these B cells to clinically approved inhibitors, such as Idealisib, Ibrutinib and Venetoclax. ESR11 will also develop protocols to initiate a CRISPR/Cas9-based screen to fine additional vulnerabilities in these B cell lines. Moreover, the student will determine how different T cell subsets can either promote or suppress lymphoma development with relevance to cancer immunotherapy.

Host: University of Cambridge (UCAM), UK

Supervisor: Klaus Okkenhaug

Doctoral programme: University of Cambridge

Envisioned secondments: CIC bioGUNE, Josep Carreras Institute

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PhD Project 12: Treg evolution in B cell lymphoma patients under Idelalisib

The PI3Kδ inhibitor, Idelalisib (IDL), is approved for chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL), but induces many toxicities. In other B-cell indolent lymphomas, clinical responses are also reported, but with fewer tolerance concerns. The reason for this high activity and fewer safety issues observed in a cohort of CLL/FL patients (treated at IUCTO) is not understood. To identify cellular mechanisms at the origin of these differential responses, ESR12 will: analyse single-cell experiments in spleen from FL or splenic marginal zone lymphoma (SMZL) patients, monitor the evolution of patient circulating immune cell population (incl. Treg) under treatment to explain activity/toxicities, investigate activity/toxicity events linked to other PI3Kδ drug and dissect molecular mechanisms linked to heterogeneity of response ex vivo.

Host: Institut national de la santé et de la recherche / Université de Toulouse III (INSERM), France

Supervisors: Dr. Julie Guillermet-Guibert and Dr. Loïc Ysebaert

Doctoral programme: Université Toulouse III – Paul Sabatier

Envisioned secondments: iOnctura, ErasmusMC

PhD Project 13: To identify PI3K vascular-related therapies which enhance immunoregulation flux

Vascular growth abnormalities are a hallmark of Pik3ca-related vascular tumours. Drugs targeting PI3Ka in tumours have proven to inhibit vessel growth, enhance hypoxia and impair antitumor immunity. ESR13 will take advantage of a collection of mouse models that allow to express diferent variants of Pik3ca oncogenic mutations (from low to high PI3K signalling) in endothelial cells, to study cell growth and immune infiltration. Vascular growth in the aforementioned mice will be followed by histological, FACS and molecular characterization by RNAseq of endothelial cells and immune populations. Upon identifying, possible targeting approaches, ESR13 will apply combinatory therapies to target vascular and immune cells.

Host: Institut de Recerca contra la Leucèmia Josep Carreras (JOSEP CARRERAS INSTITUTE), Spain.

Supervisor: Dr. Mariona Graupera

Doctoral programme: University of Barcelona

Envisioned secondments: Inserm, UCL

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PhD Project 14: To screen and analyse the drug-like profile of compounds targeting PI3K

KITHER has developed two proprietary chemical moieties that modulate PI3K signal transduction events; (1) KIT2012 which has been optimised for inhaled treatment, and (2) KIT2014 has the ability to block PI3Kg scaffolding functions. ESR14 will apply them in Cystic Fibrosis (CF) disease and the severe and lethal Idiopathic Pulmonary Fibrosis (IPF). ESR14 will establish an in vitro cellular model of CF to characterise the role of PI3Kg and of its modulation in the pathogenesis of CF. Immortalised epithelial cells carrying the most prevalent mutation found in CF patients will be used to identify the underlying mechanisms. In parallel, transgenic animals and models of obstructive (CF-like) and restrictive (IPF) airway disease will be generated to characterise the contribution of PI3K in the diverse cell subpopulations (immune cells, epithelial, fibroblasts) that participate in pathogenesis. Secretory mechanisms, ion fluxes, proliferation and membrane dynamics will be assessed

Host: Kither Biotech (KITHER), Italy

Supervisor: Prof. Emilio Hirsch

Doctoral programme: University of Torino (4 years PhD Programme)

Envisioned secondments: University of Cambridge, Josep Carreras Institute

PhD Project 15: Improving accuracy and time-to-diagnosis of rare disease by developing AI-based algorithms

Next generation sequencing technologies have accomplished the long-awaited milestone of sequencing a genome at a cost below $1000. This makes it possible that millions of people affected by rare diseases can benefit from a diagnostic genetic test. However, once genome or exome sequence is produced, variant annotation, prioritisation and ultimately interpretation in the clinical and familial context, still remains the most important and costly bottleneck. ESR15 will develop a software that incorporates Artificial Intelligence algorithms at different steps and facilitates data interpretation, so at the end, the procedure is faster, more robust, and reliable. ESR15 will develop different machine learning algorithms to improve the process key steps: 1) automation of clinical history gathering into HPO terms, 2) variant categorisation according to ACMG classification, 3) prioritisation of disease-causing mutations, in the scope of the informed phenotype and variants identified.

Host: qGenomics (qG), Spain

Supervisor: Dr. Lluis Armengol

Envisioned secondments: U-Paris, Amstersdam UMC

REQUIREMENTS:

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Eligibility criteria:

We welcome applications from PhD candidates from any country fulfilling the following criteria:

- Eligible candidates must not have resided or carried out their main activity (work, studies, etc.) in the country of their host institution for more than 12 months in the 3 years immediately prior to their recruitment by the host institution (i.e. the starting date indicated in the employment contract/equivalent direct contract).
- Eligible candidates shall at the date of recruitment by the host institution (i.e. the starting date indicated in the employment contract/equivalent direct contract), be in the first 4 years (full-time equivalent research experience) of their research careers and not have been awarded a doctoral degree.
- Eligible candidates must have a master's degree relevant for the chosen position (including biology, medicine, biochemistry, bioinformatics or a related discipline, depending on each PhD project) or its equivalent that would entitle them to a doctorate or must hold an official university qualification from a country of the European Higher Education Area with a minimum of 300 ECTs of official university studies.

Candidates must have a high level of proficiency in written and spoken English, which will be assessed with the motivation letter and the interview, respectively.

For applicants of project 3 at *Stichting Radboud universitair medisch centrum*, in Netherlands, Dutch will be required and epidemiological background will be considered

ADDITIONAL INFORMATION:

Application and selection process

The application will be done through an online application platform to be found on the PIPgen website: www.PIPgen.eu. Applications must be in English. Each applicant may apply to a **maximum of three individual research projects**.

To apply for the UCL positions, in addition to the procedures outlined here, **a further application will need to be completed via the UCL website** – this is to conform with UCL's own recruitment process. This second step is not yet available online, but we will inform candidates as soon as it opens.

Eligible applications will be ranked on the basis of CVs and merits by a selection committee. The 3 best candidates for each position will be invited for a virtual interview by 28 June-1 July 2021 where the final candidates will be selected.

Applicants with a positive evaluation but not selected will be included on a reserve list to cover eventual future positions and might be contacted at a later stage.

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Timeline

- Application deadline: 4th July 2021
- Announcement of preselection results and call for interviews: 15th July 2021
- Recruitment virtual Workshop: Short-listed candidates will be interviewed between 21-23 of July 2021.
- Announcement of pre-selected candidates: 9th of August 2021
- Communication of the final results: 13th of August 2021
- Tentative start of the fellowship: Between September 2021 and February 2022

Benefits

- 3-year full-time employment contract (salary depends on the country of the recruitment considering both local and MSCA regulations for Early Stage Researchers and their family status at the time of the recruitment).
- Enrolment in a PhD programme (In case of 4 years University Programmes, a 4th year contract will be assured).
- Shared research and innovative multidisciplinary and multisectoral training by experts and experienced trainers from two sectors (academia and industry) and two research environments (clinic and basic).
- A structured training programme consisting of soft skill courses, targeted workshops, retreats, social events and networking.
- Secondments at other institutions within the PIPgen consortium.
- Gaining experience abroad.
- Opportunities for participation in national and international meetings.
- Enlarged professional network and improved future scientific career perspective in academia and the private sector.

To apply and for further information on the PIPgen network, please visit www.pipgen.eu

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