GLIOTRAIN

European Training Network

15 New PhD Student Positions

Applications are invited from candidates of excellence wishing to pursue a PhD degree in the field of cancer precision medicine**.** Students will receive training within a pan-European academic/private sector research training network, specifically focused on brain tumour research.

Glioblastoma (GBM) is the most frequent, aggressive and lethal of all brain tumours. It has a universally fatal prognosis with 85% of patients dying within two years. New treatment options and effective precision medicine therapies are urgently required. The GLIOTRAIN European Training Network (ETN), which comprises 9 funded beneficiaries and 14 associated partner organisations from 8 countries, will train 15 innovative, creative and entrepreneurial PhD students.

The research objective of GLIOTRAIN is to identify novel therapeutic strategies for application in GBM, while implementing state of the art next generation sequencing, systems medicine and integrative multi-omics to unravel disease resistance mechanisms. Research activities incorporate applied systems medicine, integrative multi-omics leveraging state of the art platform technologies, and translational cancer biology implementing the latest clinically relevant models.

The consortium brings together leading European and international academics, clinicians, private sector and not-for-profit partners across GBM fields of tumour biology, multi-omics, drug development, clinical research, bioinformatics, computational modelling and systems biology. Thus, GLIOTRAIN will address currently unmet translational research and clinical needs in the GBM field by interrogating innovative therapeutic strategies and improving the mechanistic understanding of disease resistance. The GLIOTRAIN ETN addresses current needs in academia and the private sector for researchers that have been trained in an environment that spans translational research, medicine and computational biology, and that can navigate confidently between clinical, academic and private sector environments to progress applied research findings towards improved patient outcomes.

The programme is funded through the Horizon 2020 Marie Skłodowska-Curie Actions Programme. Selected candidates will be offered a highly competitive stipend (as per generous Marie Skłodowska-Curie Actions funding rules). *During their training each student will spend time on secondment in academic, clinical and/or private sector research institutions thus must have a willingness to travel.*

Eligibility: At the time of recruitment, the candidate must not have resided or carried out their main activity (work, studies, etc.) in the country of their recruiting organisation for more than 12 months in the 3 years immediately prior to start of the project. Short stays such as holidays and/or compulsory national service are not taken into account.

Candidate requirements: Candidates can be of any nationality, but are required to undertake transnational mobility. Candidates should ideally possess a Master's degree in a relevant academic field, however exceptional candidates holding a Bachelor's degree will be considered. Candidates must be within the first four years of his/her research career. Applications from candidates who already possess a doctoral degree will not be considered.

Potential candidates should be able to demonstrate motivation and a strong eagerness to learn. Individuals must possess excellent written, oral communication and organizational skills. In addition, applicants should have the ability both to work independently and as part of a team. Previous related research experience will be a distinct advantage. All students must be willing to travel and will be required to complete international secondments.

Funding: PhD positions are funded at the level stipulated by Marie Skłodowska-Curie Actions funding rules with stipends starting at €45,000 per annum. Final salary calculations take into account living costs of the recruiting country. Additional family allowances are available where applicable.

Application process:

- **Project(s):** applicants can select **up to two (2)** preferred projects from the list available below;
- **Required documents:** a full CV, a motivation letter including a description of previous research experiences and contact details or recommendation letters of two 2 referees. **Only documents in English will be accepted.**
- **Submission:** applicants should submit the documentation to gliotrain@rcsi.ie writing in the subject line the number of their selected projects (E.g. Projects 1 and 3) by **November 10th 2017. Successful applicants will commence their projects no later than January 2018**

Applications failing to include the requested documentation, where the candidates do not meet the eligibility criteria or which do not indicate the preferred projects WILL NOT be considered.

Selection process:

Shortlisted candidates will be invited for in-person interviews (and/ or by telephone / Skype). Positions will be offered to candidates following approval by the GLIOTRAIN co-ordinator and training committee. We will endeavour to provide feedback to unsuccessful applicants where possible.

GLIOTRAIN PhD Projects

Project 1: Validation of the APOPTO-CELL modelling environment as a superior predictor of treatment responsiveness in newly diagnosed and recurrent GBM patients

Location: Royal College of Surgeons in Ireland

Principal Investigator: Dr Brona Murphy (bronamurphy@rcsi.ie)

Collaborators: Prof Markus Morrison (University of Stuttgart, Germany), Dr Verena Murphy (Cancer Trials Ireland)

Project Summary: A major contributor to the poor survival rates of GBM patients is the extreme resistance to death-inducing treatment stimuli which GBM cells display. Our group has particular interest in the ability of GBMs to resist the programmed cell death pathways of apoptosis. We have published that a systems modelling approach (APOPTO-CELL), examining the expression of keys players within apoptotic pathways can be exploited to predict patient survival to current treatment strategies. In Project 1, the PhD student, based in RCSI, with a secondment to the University of Stuttgart, will enhance the clinical relevance of our novel systems modelling approach by quantitatively analysing a large cohort of GBM patient samples for the expression of apoptosis regulators. By integrating this analysis with our systems model, the student will examine the competency of the samples to execute apoptosis and critically, will also predict treatment responsiveness. Predictions will subsequently be validated against clinical follow up data and associations between predictions and survival will be evaluated by Kaplan-Meier estimates and Cox proportional hazards regression models. As analysis of clinical data forms an integral part of this project, the PhD student will have a unique opportunity to work on site with the national clinical trials organisation, Cancer Trials Ireland where (s)he will gain training in clinical trial design and

management. Finally, back at RCSI, the student will prepare stem cell lines from GBM tumours and test whether predictions of apoptosis competency also hold true for novel treatment combinations.

Specific Requirements:

- MSc in a in the area of Biology, Biochemistry, Mathematics, Bioinformatics, Systems Biology, or a related field,
- Experience in at least one higher programming language desirable.
- 3 Year Duration

Project 2: Development of a validated mathematical model to predict GBM responsiveness to the translationally relevant TRAIL-variant IZI1551

Location: University of Stuttgart, Germany

Principle Investigator: Prof Markus Morrison (markus.morrison@izi.uni-stuttgart.de)

Collaborators: Dr Brona Murphy (Royal College of Surgeons in Ireland), Dr Lothar Terfloth (In silico Biotechnology, Germany)

Project Summary: The University of Stuttgart, together with RCSI, recently validated a new data-driven mathematical framework that predicts apoptosis responsiveness of GBM cells to tumour necrosis factor-related apoptosis-inducing ligand (TRAIL). The University of Stuttgart has further engineered a superior 2nd generation hexavalent TRAIL-variant, IZI1551, for clinical application. In Project 2, the PhD student will conduct experimental studies on cellular signal transduction and use these data to validate a prototype systems-biology-based tool that can predict GBM responsiveness to IZI1551. Hosted at the University of Stuttgart, the PhD student will extend data-driven and deterministic mathematical models for IZI1551 responsiveness. They will study IZI1551 responsiveness for a panel of GBM cell lines as a single agent, or in synergistic combination with the blood-brain barrier permeable COXII inhibitor celecoxib. Cell death cytometry of dose combination matrices of IZI1551/celecoxib at clinically relevant concentrations as well as imaging approaches will be used to determine synergy and cell death modalities. During a 3 month secondment to In Silico Biotechnologies (Stuttgart, Germany), the PhD student will use proprietary mathematical frameworks to optimize IZI1551 production, based on predictions of improved growth conditions and media composition. Back at the University of Stuttgart, the PhD student will use these results to upscale production for use during a subsequent 6 month secondment to RCSI (Dublin, Ireland). At RCSI, GBM spheroids and fresh *ex vivo* GBM tissue (from male and female patients) will be treated and responsiveness evaluated to IZI1551. Further, TRAIL pathway proteins will be quantified from untreated GBM spheroids and *ex vivo* GBM tissue. Back at the University of Stuttgart, the PhD student will test if 3D and *ex vivo* protein data is sufficient to predict responsiveness to IZI1551/Celecoxib, thus providing clinically-relevant validation data.

Specific Requirements:

- The candidate should hold a Master's degree or equivalent and have a background in the fields of cell biology, biochemistry, systems biology (incl. experimental components) or related disciplines
- Additional experience in mathematical modeling or programming will be given preference, but is not a prerequisite
- 3 Year Duration

Project 3: Development and testing of a CNS-penetrating variant of the translationally relevant TRAIL-variant IZI1551

Location: University of Stuttgart, Germany

Principle Investigator: Prof Markus Morrison (markus.morrison@izi.uni-stuttgart.de)

Collaborators: Dr Thomas Schirrmann (YUMAB, Germany), Prof Annette Byrne (Royal College of Surgeons in Ireland)

Project Summary: The University of Stuttgart has engineered a novel, clinically relevant, anti-tumour biologic, the TRAIL receptor agonist IZI1551. However, non-invasive delivery to the central nervous system (CNS) remains a major obstacle in GBM treatment, due to the presence of the blood-brain barrier (BBB). In Project 3, the PhD student will use *in silico*, *in vitro* and *in vivo* methods to design, produce, optimise and validate a CNS-targeted variant of IZI1551 (CNS-IZI1551) by targeting receptor-mediated transcytosis at the BBB. At the University of Stuttgart they will first modify existing *in silico* models of receptor-mediated transcytosis to optimise CNS-IZI1551 delivery into the CNS. The PhD student will use these results to select optimal designs for CNS-IZI1551 followed by cloning, production and purification. They will employ an *in vitro* model of the BBB using cerebral endothelial cell lines and will characterise BBB properties such as tightness of barrier and expression of key BBB proteins. They then will assess CNS-IZI1551s for their efficacy in undergoing RMT across the *in vitro* BBB model. Seconded to YUMAB (Brunswick, Germany) the PhD student will be introduced to principles of antibody-based drug development and generate cells for the optimized production of the leading CNS-IZI1551 variant. Back at the University of Stuttgart, the PhD student will then use existing mathematical models of TRAIL responsiveness to predict CNS-IZI1551-induced apoptosis in GBM cell lines at the delivered concentrations, which will then be validated *in vitro*. Finally, seconded to RCSI (Dublin, Ireland), the student will test CNS-IZI1551 for its bio-distribution *in vivo*, including its ability to penetrate the BBB and enter the CNS.

Specific Requirements:

- The candidate should hold a Master's degree or similar and have a background in the fields of cell biology, systems biology, mathematical modelling, bioinformatics or related disciplines
- Basic programming experience is required (e.g. MatLab, R, C, java, python or similar software environments)
- Experience in biological research will be given preference
- 3 Year Duration

Project 4: Pre-clinical interrogation of checkpoint inhibitor immunotherapy in GBM implementing ultrasound (US)-induced opening of the BBB

Location: ICM Institute for Brain and Spinal Cord, France

Principle Investigator: Dr Ahmed Idbaih (ahmed.idbaih@gmail.com)

Collaborators: Prof Markus Morrison (University of Stuttgart, Germany), Racim Bouabdallah, MD (Bristol Myers Squibb, France), Frederic Sottilini (CarThera, France), Dr Maria Mancini (Champions Oncology, United States of America)

Project Summary: Immune checkpoints inhibitors (i.e. antibodies targeting CTLA4 or PDL1) have dramatically changed the prognosis of several cancers (i.e. Melanoma, Lung Cancer) (Hodi et al., 2010; Eggermont et al., 2016; Brahmer et al., 2012). Therefore, these therapeutic antibodies raised a lot of hope in treatment of glioblastoma patients. However, the blood brain barrier in the setting of brain tumors, is a major limitation to the penetration of these large therapeutic agents in the brain and the tumor for therapeutic activity (Drean et al., 2016). In Project 4, the PhD student will be seconded to USTUTT to apply agents based computational models to simulate how US-based disruption of the BBB is linked to antibody penetration. Back at ICM, PhD student will develop and characterized: (i) syngeneic models of GBM, and (ii) humanized mouse model with patient-derived cell line. After training in implementation of the BBB opening device at SME partner, PhD student will investigate: (i) brain penetration (ii) biological activity (iii) therapeutic activity of anti-CTLA-4, anti-PD1 and anti-PDL1 antibodies alone or in combination with ultrasounds-induced opening of the BBB.

Specific Requirements:

- MSc in a Biological Discipline with preference given to those candidates with experience in Immunology/Oncology.
- Experience with Molecular biology, Cell culture, Flow cytometry methods and analysis.

- In Vivo Tumour Model experience is mandatory for this position
- 4 year duration

Project 5: Anti-angiogenic Immunotherapy as a new treatment paradigm for GBM molecular subtypes

Location: Royal College of Surgeons in Ireland (RCSI Dublin City Centre Campus)

Principle Investigator: Prof Annette Byrne, RCSI Dept of Physiology & Medical Physics (annettebyrne@rcsi.ie)

Collaborators: Prof Diether Lambrechts (Vlaams Instituut voor Biotechnologie (VIB) Leuven, Belgium), Dr Maria Mancini (Champions Oncology, Baltimore, USA)

Project Summary: GBMs can be classified into subtypes with specific characteristics e.g. mesenchymal GBMs have higher vascular endothelial growth factor (VEGF)/angiogenic marker expression showing more prominent immune cell infiltration. Given the link between immune suppression and angiogenesis, targeting VEGF and immune pathways together will likely exert beneficial effects in mesenchymal GBM patients. In Project 5, the PhD student will firstly perform transcriptomic profiling of a cohort of newly diagnosed GBM samples whilst on secondment at VIB (Leuven, Belgium). Back at RCSI, gene expression data generated will be used to infer immune or stromal content of patient samples, which will be validated by immunohistochemical analyses. Finally, while seconded to Champions Oncology (Baltimore, USA) the student will be trained in the generation of humanized models (i.e. rodent models bearing a humanized immune system) which will be employed to assess anti-angiogenic immunotherapy in vivo.

Specific Requirements:

- MSc in a Biological Discipline with preference given to those candidates with experience in Tumour Biology/Oncology.
- Experience with Next Generation Sequencing (RNA Seq, Shallow Sequencing etc) methods and analysis.
- In Vivo Tumour Model experience is mandatory for this position
- 4 Year Duration

Project 6: Investigating intratumoural GBM heterogeneity in the context of antiangiogenic immune therapies

Location: Vlaams Instituut voor Biotechnologie, Belgium

Principle Investigator: Prof Gabriele Bergers (gabriele.bergers@kuleuven.vib.be)

Collaborators: Dr Edwin Spaans (Oncurious, Belgium)

Project Summary: High-resolution sequencing technologies have revealed significant inter- and intra-tumoral molecular heterogeneity in Glioblastoma (GBM), a belligerent brain tumour that is recalcitrant to most therapies. The heterogeneous nature of these tumours challenges attempts of targeted therapies. GBMs are also phenotypically heterogeneous being comprised of specific vascular niches that regulate multiple pivotal tumour properties. Intra-tumoral heterogeneity is therefore likely to be promoted by interactions between tumour cell clones and their microenvironment, with immune and other stromal factors influencing malignant progression and therapeutic resistance.

In Project 6, the PhD candidate will investigate intra-tumour heterogeneity in a genetically engineered mouse model of GBM using spatial transcriptomics, a novel technology that allows visualization and quantitative analysis of the transcriptome with spatial resolution within tissue sections. The candidate will dissect vascular tumour niches to determine the presence and interaction of the different tumour cell subpopulations with host niche constituents; i.e. the tumour vasculature and immune cells and investigate how the different niche cell types and the distinct tumour subclones respond and adapt to antiangiogenic immune therapy. Treatment will be conducted in collaboration with Oncurious where the student will acquire skills in therapeutic antibody design (ie TB-403, anti-PLGF antibody) and implementation for pharmacological studies. On return to VIB, the candidate will treat a syngeneic GBM mouse model of intratumoural heterogeneity with anti-angiogenic immunotherapies (ie anti-VEGF + anti-PDL1, anti-CTL4A, or anti-PLGF) and perform spatial transcriptomic analyses of treated tumours. This will reveal spatiotemporal behaviour of tumour subclones and the GBM environment and inform about the mechanistic underpinnings of response and adaptation to therapy.

Specific Requirements:

- MSc in a Biological Discipline with preference given to those candidates with experience in Oncology/Tumour Biology or Immunology.
- Experience with Sequencing and bioinformatics analysis are preferred
- 4 year duration

Project 7: Drug repurposing of available anti-cancer agents for precision therapy of GBM patients

Location: Erasmus University Rotterdam, The Netherlands

Principle Investigator: Dr Martine Lamfers (m.lamfers@erasmusmc.nl)

Collaborators: Prof Jochen Prehn (Royal College of Surgeons in Ireland), Mr Hennie Henrichs (Teva Pharmaceutical Industries, The Netherlands)

Project Summary: The development of new therapeutic agents generally takes many years to translate to clinically effective new treatments. One of the strategies to reduce this time frame is drug rediscovery (or repurposing). With this approach, compounds available for a specific disease are evaluated for their therapeutic efficacy in other diseases, based on more recent disease concepts and new assay methodologies. Hosted at ErasmusMC the PhD student will implement GLIOscreen® in the current project to test and validate a large panel of currently available off-patent anticancer agents (120 compounds) on in total 60 patient-derived GBM cell cultures. Systems medicine will be employed to define predictors to reponse to each of these agents. Using these systems modeling approaches, the integrated analysis of both mutational and expression data of each tumour, will facilitate the identification of key pathways in a particular tumor involved in response or resistance to specific compounds.

Specific Requirements:

- MSc in a Biological Discipline with preference given to those candidates with experience in Tumour Biology/Oncology.
- Experience with Next Generation Sequencing methods and analysis and bioinformatics.
- In Vivo Tumour Model experience is mandatory for this position
- 4 Year Duration

Project 8: Genomic biomarker driven approach to better identify GBM patient responders to SOC therapy

Location: Agilent Technologies, Belgium

Principle Investigator: Dr Jurgen del Favero (jurgen.delfavero@agilent.com)

Collaborators: Prof Diether Lambrechts (Vlaams Instituut voor Biotechnologie, Belgium), Dr Ahmed Idbaih (ICM Institute for Brain and Spinal Cord, France

Project summary: GBM is the prototypical disease where future therapies will likely depend on establishing a male or female patient's genotype and proteomic profile using robust biomarkers. The

PhD student will design NGS based bio-informatics pipeline assays for combined mutation and Somatic Copy Number Alterations (SCNAs) analysis of GBMs and will link genomic biomarkers to patient response to SOC therapy. After an academic secondment at VIB, to perform low-coverage whole-genome sequencing (WGS) to establish SCNAs on GBM samples. On return to Agilent technologies, the student will subsequently develop a broad bioinformatics platform to enable NGS analysis supporting both mutation and SCNA data. The platform will use both publically available and proprietary algorithms and will correlate SCNAs with patient disease state, prognosis and SOC syngeneic mouse model of GBM.

Specific Requirements:

- MSc in a Biological Discipline with preference given to those candidates with experience in Bio-informatics.
- Experience with Next Generation Sequencing (RNA Seq, Shallow Sequencing etc) methods and analysis.
- 4 Year Duration

Project 9: Systems-based integration and analysis of a deeply phenotyped GBM cohort correlating to 'extreme' and 'poor' responding patients

Location: Royal College of Surgeons in Ireland

Principle Investigator: Prof Jochen Prehn (jprehn@rcsi.ie)

Collaborators: Dr Alexander Kel (geneXplain, Germany), Dr Ahmed Idbaih (ICM Institute for Brain and Spinal Cord, France).

Project Summary: The project will molecularly phenotype and functionally interrogate patient cohorts correlating to 'extreme' and 'poor' GBM responders. The strategy will employ the process of 'natural pre-selection' to identify key differences in the underlying biology facilitating identification of new functional master drivers. Natural pre-selection been successful in describing metabolic aberrations leading to diabetes and obesity, but has thus far not been employed in GBM. To identify novel GBM resistance mechanisms, the PhD student 9, hosted at RCSI will focus on deep phenotyping a cohort of gender balanced n=100 GBM patients grouped according to favourable or unfavourable clinical outcome despite similar (histo)pathological features. The PhD student will be seconded to UPMC for 3 months to identify and prepare a collection of n=100 GBM samples for subsequent analysis. On return to RCSI, (s)he will commence molecular subtyping of this cohort of 'poor' and 'extreme' responders to include WES, RNA seq, metabolomic profiling (NMR

spectroscopy) and reverse phase protein array -based protein and phosphoprotein analysis (>150 validated antibodies). The PhD student will employ deterministic models developed by RCSI to quantitatively identify key biological differences between 'poor' and 'extreme' responders, and to relate these differences to GBM subtypes. Subsequently during a 5 month secondment to SME beneficiary GEX, PhD student 9 will link transcriptomic profiles to master transcription regulators and upstream, targetable signalling pathways, Back at RCSI, (s)he will integrate outputs from molecular profiling, deterministic systems modelling and GEX platform analysis to define specific, targetable master drivers of 'poor' and 'extreme' responders and their interaction with key signalling pathways and GBM subtypes.

Specific Requirements:

- MSc or BSc in Bioinformatics / Human Genetics / (Bio)Engineering or a related discipline with preference given to those candidates with experience in Tumour Biology/Oncology.
- Experience with Analysis of Genomics Data / Next Generation Sequencing (RNA Seq, Shallow Sequencing etc) or Proteomics data.
- Programming skills and/or Statistical Analysis Methods are of advantage
- 4 Year Duration

Project 10: Multi-scale mathematical modelling of non-Darwinian dynamics in therapy-induced drug resistance in GBM

Location: Royal College of Surgeons in Ireland

Principle Investigator: Dr Marc Sturrock (marcsturrock@rcsi.ie)

Collaborators: Dr Alexander Kel (geneXplain, Germany)

Project Summary: The propensity of GBM towards genetic mutations often allows treatment-resistant GBM to arise. However, even without genetic mutations, fitness selection processes can expand resistant variants. In Project 10, the PhD student will begin by developing holistic ordinary differential equation models of gene expression profiles which are known to play a role in the emergence of GBM drug resistance such as those involving multidrug resistance protein 1 and B-cell genes. This will be achieved using proprietary signal transduction pathway and gene regulatory network platforms (TRANSFAC® and TRANSPATH™) while seconded at GeneXplain (Wolfenbüttel, Germany). Returning to RCSI the student will calibrate these models using RNAseq data from the GLIOTRAIN biobank. Finally stochastic analogues of these models will be simulated using a stochastic simulation algorithm and inserted into a second model scale which keeps track of cell growth, division and partitioning. The model will be simulated under SOC treatment regimens and the

resultant emergence of a subpopulation of resistant cells will be analysed to delineate resistance mechanisms and propose novel treatment strategies.

Specific Requirements:

- MSc in Applied Mathematics/Mathematical Biology/Systems Biology/Computational Biology/Biophysics/Computer Science with preference given to those candidates with experience in gene regulatory network or cancer modelling
- Experience with fitting models to data e.g. using Bayesian parameter estimation techniques (MCMC, ABC etc.)
- Experience with agent based models or stochastic simulation algorithms would be beneficial
- Scientific computing skills in C / Python / Julia
- 3 Year Duration

Project 11: Single-cell RNA-sequencing in the context of space and time to interrogate tumour microenvironment (TME) impact on therapy response

Location: Vlaams Instituut voor Biotechnologie, Belgium

Principle Investigator: Prof Diether Lambrechts (diether.lambrechts@vib-kuleuven.be)

Collaborators: Dr Jurgen del Favero (Agilent Technologies, Belgium)

Specific Requirements:

- MSc in a Biological Discipline with preference given to those candidates with experience in Tumour Biology/Oncology
- Genuine Interest in Next Generation Sequencing methods and analysis
- 4 Year Duration

Project 12: Interrogating intratumoural heterogeneity and disease resistance mechanisms by scRNA-Seq in intracranial human GBM PDX models

Location: Luxembourg Institute of Health, Luxembourg

Principle Investigator: Prof Simone Niclou (Simone.Niclou@lih.lu)

Collaborators: Dr Andreas Kremer (Information Technology for Translational Medicine [ITTM], Luxembourg)

Project Summary: My laboratory has established unique mouse models of Glioblastoma derived from patient tumours, which provide an excellent tool to address tumour-host interactions and

undertake functional studies on drug response. In this project we will generate such patient-derived xenograft (PDX) models of GBM and apply advanced flow cytometry followed by single cell sequencing and integrative systems-level bioinformatics data analysis to decipher how tumor cells adapt to the microenvironment and respond to drug treatment. This project will shed light on tumor adaptation and resistance mechanisms at the single cell level.

Specific requirements:

- Master in Biological Sciences, ideally with a focus on cancer genomics or cancer biology
- Strong background in molecular biology
- Affinity to omics data and bioinformatics is a plus
- 4 year duration

Project 13: Integrative genomic analysis of drug resistance in GBM using advanced 2D and 3D models

Location: Erasmus University Rotterdam, The Netherlands

Principle Investigator: Prof Sieger Leenstra (s.leenstra@erasmusmc.nl)

Collaborators: Dr Jos Joore (Pepscope, The Netherlands and Mimetas, The Netherlands).

Project Summary: One of the major factors for the dismal prognosis of patients diagnosed with glioblastoma is drug resistance. To tackle this problem tumour models for studying resistance are mandatory. In recent years we developed a few models to study this. Prolonged drug exposure is then applied to evoke resistance. By genomic and proteomic analysis before and after the occurrence of resistance the molecular mechanisms can be revealed and targets to overcome resistance may be identified. Using systems modelling approaches, the integrated analysis of both genomics and proteomics data of each cell culture, will help expose the escape routes in resistant tumours and identify targets for combinatorial or sequential therapy. Validation of these candidate second drugs will be performed using the GLIOscreen® protocol. To study drug resistance in the broadest sense it is of utmost important to address intratumoral heterogeneity and influences of the micro-environment. Therefore, we developed different 3D culture techniques that will be applied in the current project.

Specific Requirements:

- MSc in a Biological Discipline with preference given to those candidates with experience in Tumour Biology/Oncology.
- Experience with Next Generation Sequencing methods and analysis and bioinformatics.
- In Vivo Tumour Model experience is mandatory for this position
- 4 Year Duration

Project 14: Modelling therapeutic resistance in GBM using multi-omic computational models

Location: geneXplain, Germany

Principle Investigator: Dr Alexander Kel (alexander.kel@genexplain.com)

Collaborators: Dr Martine Lamfers (Erasmus University Rotterdam, The Netherlands), Prof Diether Lambrechts (Vlaams Instituut voor Biotechnologie, Belgium)

Please contact Dr Alexander Kel for information regarding this project.

Project 15: Systems methods for analysis of heterogeneous GBM datasets towards elucidation of inter-tumoural resistance pathways and therapeutic new targets

Location: ITTM S.A., Luxembourg

Principle Investigator: Dr Andreas Kremer (andreas.kremer@ittm-solutions.com)

Collaborators: Prof Diether Lambrechts (Vlaams Instituut voor Biotechnologie, Belgium), Dr Verena Murphy (Cancer Trials Ireland), Dr Martine Lamfers (Erasmus University Rotterdam, The Netherlands).

Project Summary: Integrating heterogeneous 'omics data constitutes not only a conceptual challenge but also a practical hurdle. In Project 15, the PhD student will firstly use publicly available multi 'omic human GBM datasets and identify the most representative data points for each of the main disease pathways, and will map these to disease processes and biological pathways using to identify and visualize novel resistance mechanisms. In parallel, the PhD student will develop a GBM specific data management system to allow data access monitoring including simultaneous, or sequential access to multi-'omic datasets by automated analytical pipelines. Importantly, during a 5-month secondment to clinical trial organization partner CTI, the PhD student will analyse GLIOTRAIN clinical data sets within the platform. Back at ITTM, newly identified targetable pathways will be validated using the GLIOTRAIN data set. Next, the PhD student will complete an academic secondment to VIB for 4

months to perform targeted RNA re-sequencing of at least 10 newly identify GBM related druggable targets (selected in collaboration with clinical experts at EMC).

Specific Requirements:

- MSc in a Biological Discipline with preference given to those candidates with experience in Bioinformatics or Computational Biology.
- Experience with biological data management and knowledge of biological descriptive languages (SMBL, openBEL or BioPAX) is a strong advantage.
- Basic experience in programming in a scripting language is necessary for this position
- 4 Year Duration

Informal Inquires:

For informal inquiries regarding the application and eligibility questions, contact gliotrain@rcsi.ie. For informal queries regarding specific projects contact the Principal Investigator directly.

Best of luck!

GLIOTRAIN Recruitment Team