Translational SYStemics (TranSYS)
- Personalized Medicine at the Interface of Translational Research and Systems Medicine -

Summary

TranSYS, coordinated by K. Van Steen (KU Leuven), will recruit 15 ESRs (Early Stage Researchers) to highly skilled jobs in the new area of Systems Health developing tools and approaches to exploit large and complex datasets, to advance Precision (Personalised) Medicine in several disease areas. The training programme and experience of different international research environments cuts across traditional data and life sciences silos. The emphasis on translational research will support new collaborations between academics and the pharma and health analytics sectors. Our ESR projects will advance the state of the art on biomarker discovery, improve understanding of disease-specific molecular mechanism and target identification for optimal diagnostics, disease risk and treatment management, refine data generation and their management (including warehousing, disease specific and standardised approaches for data processing, visualisation and model development) leading to improved clinical study design, clinical sampling and more targeted therapeutics. This ETN (European Training Network) will internationalise participants, and leverage EC (European Commission) and industry sponsorship, to structure and expand the unique training programme and advance emerging research areas, combining wet-lab, clinical and Big Data resources with computational and modelling know-how.

To achieve a paradigm shift in research training this ETN brings together international leaders in Preclinical Science & Molecular Medicine, Systems Analytics, and Targeted Therapeutics, from academia and industry. These experts are ideally positioned to develop the proposed training programme and deliver a highly-trained workforce of next generation scientists, with the right mind-set, knowledge and skills, at the interface of Translational and Systems Medicine. The TranSYS training programme is designed to addresses a critical skills gaps that is currently a bottle- neck to advancing Precision Medicine.

Projects and objectives

Fellow	Host institution	Country	PhD awarding institution	Project title	Main PI contact	Secondment partners
ESR 1	KU LEUVEN (Leuven University)	BELGIUM	KU LEUVEN (Leuven University)	**Development of individual-specific molecular networks**	K Van Steen	INSTITUT PASTEUR, THE GOLDEN HELIX FOUNDATION

Objectives: Describing a system implies describing its behavior and important control mechanisms that regulate this behavior. Crucial in this process are interactions, which may occur at different levels or scales, and thus network theory and network visualization are increasingly being used to understand biological mechanisms operating in human systems. However, an individual, especially when in poor health, is likely to deviate from the “norm” in human systems. In this project, we wish to develop omics data integrative gene-based networks to enhance PM. Such a network would enable the identification of gene modules that are subject-specific (in network nodes/edges) and comprise multi-layer cellular information. It goes beyond existing work in that genes are considered to be complex multi-omics systems, and that statistical significance is assessed for individual-specific nodes/edges (in contrast to f.i. Menche et al. 2017 and Kuijjer et al. 2018). We aim to achieve our goal by building upon the aforementioned references and our work on gene representations using diffusion kernels and network theory (Fouladi et al. 2018). Personalized gene omics-integrative signatures will primarily be derived by combining genome, transcriptome and epigenome data for complex diseases with an inflammatory component.

ESR 2	KU LEUVEN (Leuven University)	BELGIUM	KU LEUVEN (Leuven University)	**Hunting for patient subtypes through image-based phenotypes as biomarkers for major gene effects in medical disorders**	K Van Steen	BARCELONA SUPERCOMPUTING CENTER, LIFEGLIMMER GMBH
Objectives: To develop a framework for gene-centric image data integration analytics and support a patient stratification strategy that identifies major gene effects with potential applications in a variety of medical disorders. This expands our previous work on rare monogenetic/ complex diseases in craniofacial and neurodevelopmental disorders, using available extensive datasets of different imaging modalities on individuals and patient groups. Mathematics, statistical genetics and deep learning in image analysis (potentially non-linear data-dependencies) will enable data-driven phenotyping from images for patient diagnostics, and stratified screening/subtyping.						
ESR 3	ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM	NETHERLANDS	ERASMUS UNIVERSITY ROTTERDAM	**GDPR regulation in translational medicine**	P van der Spek	DELOITTE CONSULTING BV, SHIVOM
Objectives: First results on integrated omics profiling of melanoma patients, in particular primary and metastasized skin cancer patients, are promising and seem to generate interesting biomarkers with therapeutic potential. The main aim of this project is to develop a patient stratification strategy based on multi-omics data bases and a tool that enables a reliable classification of clinically relevant disease subtypes via advanced pattern recognition that can be readily translated to clinic (e.g., dermatology). Day-to-day problems in the clinic focusing on getting the right drug into the right melanoma patient are taken as case study. To achieve our goals, we will expand on previous work performed by the department of bioinformatics, pathology, clinical genetics and dermatology.						
ESR 4	KU LEUVEN (Leuven University)	BELGIUM	KU LEUVEN (Leuven University)	**Developing a precision medicine ethics, between personal empowerment and collective responsibility**	K Dierickx	FUNDACION CENTRO NACIONAL DE INVESTIGACIONES ONCOLOGICAS CARLOS III, THE GOLDEN HELIX FOUNDATION
Objectives: Proponents offer four ways in which their approach to medical diagnosis and health care improves upon current practices, arguing that it is more 'personalised', 'predictive', 'preventive' and 'participatory' than the medical status quo. This evolution in the direction of PM however implies ethical issues that differ from those in traditional clinical practice and research such as the attempt to control the impact of the 'data tsunami', the increase of 'variants of unknown significance', the rise of stratified medicine, the tension between individual empowerment on the one hand, and the need of medical expertise and authority on the other hand, the tension between enhancing individual interests and public health interventions for collective benefit. The proposed project will address these ethical challenges and 1) review the scientific literature in order see what the social and ethical ramifications are of the promises of PM; 2) interview key stakeholders (including scientists, translational researchers, clinician researchers, policy makers, funders) in order to clarify and to deal with the moral questions of PM; 3) and develop a PM ethics and recommendations that deal in a proper way with this new evolution. The envisaged qualitative methodology builds on work of Kitzinger (1995) and Hsieh and Shannon (2005) and acquired in-house expertise (Christenhusz et al. 2015; Hens et al. 2016).						
ESR 5	UNIVERZA V LJUBLANI	SLOVENIA	UNIVERZA V LJUBLANI	**Personalized molecular signatures for modulating**	D Rozman	UNIVERSITAIR MEDISCH CENTRUM GRONINGEN, INSILICOTRIALS

				progression of metabolic liver disease (NAFLD) to hepatocellular carcinoma		TECHNOLOGIES S.R.L.
Objectives: NAFLD currently suffers from the absence of treatment strategies which led to dramatic rise of liver cancer (HCC). Without treatment, HCC is fatal, with a 5-year survival of only five percent. To bridge this gap, the ESR 5 project will: 1) Integrate the public available datasets of well-defined NAFLD and HCC patient cohorts to propose novel molecular signatures of progressive NAFLD; 2) Evaluate in this patients the genetic variation to drug and metabolic stress response; 3) Experimentally validate and refine signatures (focused on cholesterol-linked transcription factors) in histologically staged liver disease; 4) Construct personalized models of liver disease management. The proposed targets will be integrated and validated within the personalized *SteatoNet* models, which will be used to identify a wider scope of NAFLD targets and identify patients at risk for adverse drug effects.						
ESR 6	UNIVERSITE DU LUXEMBOURG	LUXEMBOURG	UNIVERSITÉ DU LUXEMBOURG	**Dissecting cellular heterogeneity of Parkinson's disease (PD) related iPS cells during aging by integrated single cell transcriptomics and imaging analysis to identify disease modifiers**	A Skupin	INSTITUT PASTEUR, DELOITTE CONSULTING BV
Objectives : Recently established patient derived iPS cell approaches typically neglect the effect of aging by working with freshly differentiated cells. The proposed project will address this challenge using our PD based iPS cell collection and 1) Characterizing cellular heterogeneity during differentiation and aging of personalized iPS cells by integrating microscopy with single cell RNAseq analysis; 2) Developing a bioinformatics pipeline to identify potential disease modifiers based on network analysis and imaging based validation; 3) Integrating the obtained data into a dynamic model of cell differentiation and aging in neurodegeneration.						
ESR 7	FUNDACION CENTRO NACIONAL DE INVESTIGACIONES ONCOLOGICAS CARLOS III	SPAIN	UNI MADRID	**Personalized approaches to modulate tumor behavior using vitamin D3**	F Real	KATHOLIEKE UNIVERSITEIT LEUVEN, SHIVOM
Objectives: 1) to establish a biobank of blood and tumor samples from patients prior to and after administration of vitamin D; 2) to assess the effects of vitamin D administration on expression of tumor-relevant proteins and to validate the pharmacological effects by assessing expression of vitamin D receptor target genes in blood leukocytes; 3) to assess at the transcriptome-wide level the changes in gene expression in tumor and identify genetic profiles associated with vitamin D administration, including bioinformatics analysis of the data; and 4) to identify clinical and molecular variants associated with the response to vitamin D. This information will be crucial to provide the basis of subsequent clinical trials in which the effect of vitamin D on the recurrence of bladder cancer is tested with the aim of increasing patient cure rate.						
ESR 8	INSTITUT PASTEUR	FRANCE	UMPC-SORBONNE UNIVERSITÉS	**Integrative modelling of autoimmune diseases**	B Schwikowski	KATHOLIEKE UNIVERSITEIT LEUVEN, UNIVERSITAIR MEDISCH CENTRUM GRONINGEN, INSILICOTRIALS TECHNOLOGIES S.R.L.

Objectives: To develop dimensionality reduction (DR) techniques that project large publicly available autoimmune-related transcriptomes and associated clinical data (i.e., from Lupus, Rheumatoid Arthritis) into a common low-dimensional space (the "AutoImmune Map (AImap)"). The structure of the low-dimensional space will be informed by high-quality, multilevel, immunoprofiling data from the Milieu Intérieur cohort of 1000 healthy donors (http://www.milieuinterieur.fr) that provides a highly resolved atlas of inter-individual variation at the level of responses to elementary and complex immune stimuli. The proposed project is the first to integrate different autoimmune-related blood transcriptomes in a semantically rich low-dimensional subspace, towards a molecular taxonomy of autoimmune diseases (cf. Barturen et al. 2018, Nat. Rev. Rheumatology). AImap will thus provide a novel, powerful basis for characterizing patient variation, discovering genetic associations, patient subclasses, and prognostic and predictive markers.

ESR 9	BARCELONA SUPERCOMPUTING CENTER	SPAIN	UNIVERSITAT DE BARCELONA	**Patient-centric data integration framework for highly dimensional data**	N Pržulj	UNIVERSITE DU LUXEMBOURG, QIAGEN AARHUS AS (ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM)

Objectives: PM proposes to individualize the practice of medicine based on patients' genetic backgrounds, their biomarker characteristics and other omics datasets including exposure. ESR9 will build upon our previous work on network science, data integration and PM to propose a patient-centric data integration framework that enables all of the following: (1) improved patient stratification (allowing for predicting disease outcomes with more confidence), (2) uncovering molecular bases of diseases (molecular mechanisms, disease genes, biomarkers), and (3) personalized treatment predictions (drug repurposing). In practice, the mutational data will be mapped onto molecular networks and graphlet-based approaches will be utilized for mining for medically relevant signals. All data will be integrated using non-negative matrix factorization based approaches (Zitnik et al 2013; Gligorijevic et al. 2016) into a unified framework from which additional knowledge will be mined. Unlike existing approaches that only represent and integrate biological data as networks, we will thus also consider alternative data representation, such as hyper-networks and simplicial complexes that can capture the multi-scale organization of the data.

ESR 10	SHIVOM	UNITED KINGDOM	KU LEUVEN (Leuven University)	**Development of Clinical Blockchain Network**	D Baker	UNIVERSITE DU LUXEMBOURG, KATHOLIEKE UNIVERSITEIT LEUVEN

Objectives: This project will look into clinical aspects of using genome data linked to clinical decision making processes such as SnoMed and HL7, and build ways for third parties to control and own their data and allow access to it using a Token system. The steps involved include: (1) developing the project protocol and documentation along with identifying 30 patients in the UK and 70 patients in Nigeria for Point-of-Care sequencing, (2) developing the necessary regulatory frameworks and finalizing all compliance and ethical submissions, following feasibility analyses, (3) collecting, processing and analysing samples from enrolled multi-generational patients with Sickle Cell Disease, (4) closely working together with medical professionals, pharma and biotech companies to present the value proposition of the product and encourage its wide-spread use, (5) use results as guidance for conducting economic impact analysis of treatment decisions.

ESR 11	BIOMAX INFORMATICS AG	GERMANY	LUDWIG-MAXIMILIANS-UNIVERSITAET MUENCHEN	**Identification of biological subtypes related to treatment resistant depression**	M Butz-Ostendorf	BARCELONA SUPERCOMPUTING CENTER, MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN EV

Objectives: Depression is among the top disorders associated with years lost to disability, treatment options are not guided by underlying pathobiology but mainly based on trial and error, leading to long lag-times of treatment response in over 2/3 of the patients and the development of treatment resistance in over 10%. This project will identify biologically-defined clusters of depressed patients related to their response to antidepressant treatment. For this, psychiatric symptom severity at baseline and following antidepressant treatment will be analyzed together with genetic, gene expression, DNA methylation, structural

neuroimaging, laboratory and neuropsychological data. Data distribution and the suited type of analysis will be evaluated to identify biological features associated with different treatment outcome. This project will use an existing dataset of over 1400 depressed patients. This approach will allow to identify biologically distinct classes of patients that may benefit from distinct interventions and shed light on pathobiological mechanisms in depression.

ESR 12	UNIVERSITAIR MEDISCH CENTRUM GRONINGEN	NETHERLANDS	UNIVERSITAIR MEDISCH CENTRUM GRONINGEN	**Multi-omics analysis to delineate drug-response pathways**	C Wijmenga	LIFEGLIMMER GMBH, FUNDACION CENTRO NACIONAL DE INVESTIGACIONES ONCOLOGICAS CARLOS III

Objectives: Response to drugs is highly heterogeneous. On average medication works in only 25% of cases, and efficacy varies between patients. ESR 12 will develop stratification rules for individuals, based on genetics. For this to be effective, deep understanding of the role of drug-metabolizing SNPs in drug response pathways, and interactions with pertinent biological mechanisms and disease pathways is necessary. 1) To expand on this by investigating the molecular pathways in predicted responders and non-responders using multi-omics data (genomics, RNA-seq, methylation, metabolomics, microbiome). 2) To exploit a population-based cohort (cross-sectional) of ~1500 individuals (LifeLines-Deep – Tigchelaar et al. 2015) for which the multi-omics data have been generated already and from which 1000s of phenotypes are known, using PheWas analysis. 3) Stratify individuals based on existing knowledge about the impact of genetic variation on drug response and investigate the downstream biological consequences in a wealth of molecular parameters. At the same time, the drug metabolizing SNPs will be assessed for any impact on other clinical phenotypes.

ESR 13	MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN EV	GERMANY	LUDWIG-MAXIMILIANS-UNIVERSITAET MUENCHEN	**Understanding stress-responsive molecular networks**	E Binder	BIOMAX INFORMATICS AG, KATHOLIEKE UNIVERSITEIT LEUVEN, QIAGEN AARHUS AS (ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM)

Objectives: Exposure to stressful life events is one of the strongest risk factors for psychiatric disorders, but also contributes risk for a number of medical disorders. These stressful events are difficult to measure objectively. To nevertheless investigate how genetic variants may modify the impact of the environment a stimulated QTL approach can be adopted, in which genetic variants are identified that alter the transcriptional response to a hormonal mediator of the stress response (Arloth et al. 2015). A main mediator of the stress response is the glucocorticoid receptor (GR), a nuclear receptor with transcription factor function. Understanding the interplay of genetic and epigenetic factors that moderate an individual's transcriptional response to GR could aid prevention of stress-related disorders and help to identify individuals at high risk for stress-related disorders. Building on our own published results on stress-moderating variants shown to associate with risk for psychiatric disorders (Arloth et al. 2015; Elbau et al. 2018), the aim of this project is to 1) integrate multi-omic datasets of GR response. LCLs of individuals carrying either high or low polygenic load of variants associated with either strong or weaker transcriptional GR response will undergo RNA-seq, DNA methyl-capture Seq, GR-ChIP Seq and HiC-Seq to understand the molecular underpinnings of how common genetic variants alter GR-response. 2) The regulatory capacity of these variants will be investigated using STARR-Seq. This approach will allow to identify mechanisms of differential cellular stress response and to refine a SNP set predictive of stress-susceptibility by identification of the functional variants. This information will be summarized in functionally informed, experimentally weighted polygenic stress score to apply to clinical cohorts.

ESR 14	THE GOLDEN HELIX FOUNDATION	UNITED KINGDOM	UNIVERSITY OF PATRAS	**Standardization of disease and population-specific genotyping panel for preemptive pharmacogenomics:**	G Patrinos	UNIVERZA V LJUBLANI, NOVADISCOVERY SAS, ERASMUS UNIVERSITAIR

				Towards population pharmacogenomics		MEDISCH CENTRUM ROTTERDAM
Objectives: This project will develop and standardize disease and population-specific genotyping panels for preemptive pharmacogenomics. We will expand on our previous work, consisting of (a) the first pan-European study on clinical pharmacogenomics in Europe and (b) the delineation of the different prevalence of pharmacogenomics biomarkers in different populations among the same racial group. ESR 14 advance the knowledge and challenges by (a) developing population-specific genotyping panels for preemptive pharmacogenomics, especially for developing European countries and (b) to define disease-specific pharmacogenomic panels (e.g. cardiovascular diseases, cancer, neuropsychiatric disorders, etc). These panels will be accompanied by a dedicated web-based translational tool to retrieve, in a dynamic manner from regulators guidelines and make them available to physicians for optimizing drug prescriptions for patients based on their pharmacogenomic testing results. We will adopt a truly multidisciplinary approach, including genome informatics, A.I. and machine learning. ESR 14 will also perform economic evaluation to determine the cost-effectiveness of these panels towards reimbursement of these assays and the reduction of the overall healthcare costs.						
ESR 15	LIFEGLIMMER GMBH	GERMANY	UNIVERZA V LJUBLANI	**Developing and demonstrating data mining and A.I. tools to betterunderstand patient heterogeneityand assist patient stratification**	V Martins dos Santos	UNIVERZA V LJUBLANI, ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM
Objectives: Instead of creating new data, it is often easier, more cost-effective and in many cases even more productive to make use of the data that is already present and that just waits to be collected, harmonized and analyzed from a different viewpoint. Many public databases, e.g. dealing with omics data or clinical studies, provide so called Application Programming Interfaces (APIs) for fast, easy and most importantly automated access of their data. The objectives are to use this “hidden” potential in already created data by 1) structuring the database for related samples; 2) designing and developing a data mining tool that accesses, collects and harmonizes data via those APIs and makes it easily usable for further downstream interpretation/analysis; 3) implementing an artificial intelligence algorithm that would classify automatically a specific sample or that would detect a potential misclassification; 4) undertaking proof of concept case studies using Decipher CNV data of patients suffering from developmental neurological malformations that might hit/overlap with the Encode data and also using metabolic liver pathologies. Interpretation focuses on patient similarity, heterogeneity aiming on data re-use for personalized medicine. This will integrate the extent the collected data from various open access data sources aiming on contributing to a better understanding of patient similarity and or heterogeneity for personalized medicine.						

Recruitment

TranSYS wishes to reflect the diversity of society and thus welcomes applications from all qualified candidates regardless of personal background. Recruitment targets ESR backgrounds in 1) Lifesciences; 2) Engineering sciences and (3) Maths and Computational Modelling. In total 15 early-stage researchers will be recruited that will work at the 13 beneficiaries all across Europe. We expect that applicants hold a university degree that qualifies them for doctoral studies at their recruiting organization. Solid written and oral communication skills in English are prerequisites of any successful application (typically IELTS min. 7, TOEFL internet-based min. 90 or similar level as proven by other tests). Every applicant can apply for up to three ESR positions (first, second, third choice) from the list above.

Application details

All applications must be submitted before 31 August 2019 (midnight CET). Only applications for which the following information has been uploaded will be considered:

- Cover Letter, describing your motivation to apply, your research career goals, skills and experience, and your preferred top 3 ESR positions (rank 1= your first option).

- CV
- Diploma and transcripts of records (BSc and MSc)
- Full contact details of two reference persons
- Documentation of English language qualifications
- Other information for consideration (e.g., a list of publications if applicable)

You can apply via this link: https://h2020transys.eu/recruitment/

Additional info

Recruitment process

Only applications in English are considered. The board of the network will evaluate all applications, and the top-ranked candidates will be invited for interviews.

Formal requirements and eligibility

At the time of commencement, it is required that the candidate has not been awarded a doctorate degree and is within the first 4 years (full-time equivalent) of his/her research career. Furthermore, the candidate must not have resided or carried out her/his main activity (work, studies, etc.) in the host country for more than 12 months in the 3 years immediately prior to his/her recruitment. Short stays, such as holidays, are not taken into account. The candidate is required to spend part of her/his assignment at other institutions in the TranSYS consortium on secondments.

Terms of employment

Attractive 3-year full-time employment contract in accordance with the MSCA regulations for early stage researchers of the European Commission - continuation after the first year is dependent upon a positive evaluation.
Enrolment in a PhD program whereby PhD tuition fee is paid by project.
Supervision by recognized experts and access to (beyond) state-of-the-art research and pilot-scale infrastructure.
Training in complementary skills via participation at local and network-based events.
Terms of appointment and payment according to the rules and regulations laid down by European Union's Horizon 2020 Marie S. Curie Innovative Training Networks and regulations followed by the host institution.

Working conditions

All beneficiaries will be full-time employed at their (host) institution. The researchers are expected to conduct secondments at other network partners, as planned by the main host.