

JOINT TRANSNATIONAL CALL FOR PROPOSALS (2018) FOR
“RESEARCH PROJECTS ON PERSONALISED MEDICINE – SMART COM-
BINATION OF PRE-CLINICAL AND CLINICAL RESEARCH WITH DATA
AND ICT SOLUTIONS”



FULL-PROPOSAL APPLICATION FORM

Please note:

- Proposals that do not meet the national/regional eligibility criteria and requirements will be declined without further review.
- All fields must be completed using "Calibri font, size 11" characters, single-spaced.
- Incomplete proposals (proposal missing any sections), proposals using a different format or exceeding length limitations of any sections will be rejected without further review.
- In case of inconsistency between the information registered in the submission tool and the information included in the PDF of this application form, the information registered in the submission tool shall prevail.
- Refer to the “GUIDELINES FOR APPLICANTS” for information about the proposal structure.
- Once completed, the full-proposal must be converted in a single PDF document before being uploaded to the submission website.

CHECKLIST FOR THE COORDINATOR:

In order to make sure that your proposal will be eligible to this call, please collect the information required (on the "Call Text", "Guidelines for applicants" and through your contact point) to tick all the sections below before starting to complete this application form.

- **General conditions:**

- ☒ The project proposal addresses the **AIM/s** of the call.
- ☒ The project proposal addresses **at least one module out of each major research area**.
- ☒ I am aware of the **national/regional requirements** of the corresponding funding organisations.
- ☒ Positive evaluation of the pre-proposal and invitation to submit the full-proposal.

- **The composition of the consortium:**

- ☒ The project proposal involves at least 3 eligible research groups from at least 3 different countries participating in the first ERA PerMed joint transnational call.
- ☒ The project coordinator institution is eligible to be funded by one of the participating funding organisations.
- ☒ The project consortium is not involving more than two partners from the same country participating in the call (see "Guidelines for applicants" for specific national/regional regulations).
- ☒ The project proposal involves a maximum of 6 partners.
- ☐ The project proposal involves a maximum of 7 partners after inclusion of a partner coming from an underrepresented country: Canada (FRQS, CIHR), Croatia (MSE), Estonia (ETAg), Germany (Saxony), Italy (Lombardy, FRRB), Romania (UEFISCDI), Spain (GN), Spain (CDTI), Turkey (TUBITAK).
- ☒ The project proposal involves maximum one research group with own funding.

- **Eligibility of consortium partners:**

- ☒ I have checked that no partner of this consortium is a member of the ERA PerMed Network Steering Committee (NSC), Peer Review Panel (PRP), Call Steering Committee (CSC) or Call Advisory Board.
- ☒ I have checked that each partner involved in the project proposal is eligible to receive funding by his/her funding organisation.
- ☐ For the partner that is not eligible for funding, I have enclosed in the proposal a signed (written) statement declaring that they will be able to run the project with their own resources.
- ☐ Slovenian partners asking funds to the Ministry of Education, Science and Sport (MIZS) have submitted the requested duly amended national document in parallel. In case, the national document is NOT DULY AMENDED, the Slovenian partners will be declared ineligible.
- ☐ Lombardy, FRRB (only in case of inclusion of an additional partner from Lombardy, FRRB, as underrepresented country/region): Lombardy research institutions which request funds to the Regional Foundation for Biomedical Research (FRRB) shall submit to the Funding Agency the requested regional document 10 days before the submission deadline.

- **Submission of the same research project to other calls:**

Is this submitted project subject to another evaluation process? ☐ Yes ☒ No
 This includes other joint transnational calls (e.g. NEURON, E-RARE, ERA-CVD, JPND, JPI HDHL, EuroNanoMed, ERACo-SysMed and others).

If YES, please specify:

GENERAL INFORMATION

Project title

Rational antiepileptic drug selection by combining gene network and ICT analysis

Acronym (max. 15 characters)

RAISE-GENIC

Project duration (months)

36

Total project costs (€)*

1,162,341

Total requested budget (€)*

996,197

**Please make sure that the same figures are entered in the sections that need to be completed online (pt-outline submission tool). Thousand separators and whole numbers should be used only (e.g. 200.000).*

1.1 PROPOSAL CLASSIFICATION

Please tick the appropriate boxes to specify the category of your application.

Each project proposal must tackle the two major research areas:

The **Research Area 1** and the **Research Area 2** by addressing at least one module out of each research area:

Research Area 1: “Validation, pre-clinical and clinical biomedical research – Translating Basic to Clinical Research and Beyond”

Module 1A: Pre-clinical Research

☒ Yes

☐ No

Module 1B: Clinical Research

☒ Yes

☐ No

Research Area 2: “Data analysis, management and protection – Integrating Big Data and ICT Solutions”

Module 2A: Data and ICT – Enabling Technology

☒ Yes

☐ No

Module 2B: Data and ICT – Towards application in health care

☒ Yes

☐ No

1.2 KEYWORDS (FROM 5 UP TO 7)

Please list 5 to 7 keywords describing your proposal.

Epilepsy, antiepileptic drug, precision medicine, genetics, biomarker, iPSC, big data

1.3 SCIENTIFIC ABSTRACT (MAX. 2,000 CHARACTERS, WITH SPACES)

Please give a comprehensive and readable summary of the most important aims and methods of the project. Please note that if the project is selected for funding this abstract is to be published in the newsletter and on the funding organisations' websites.

Epilepsy is one of the most frequent chronic neurological disorders with a major impact on quality of life. Currently, less than 50% of patients become seizure free with the first antiepileptic drug (AED). The identification of factors allowing the selection of the AED with the best chance of success in individual patients (precision medicine) would revolutionise epilepsy treatment. We aim to achieve this by two data-integrative (big-data) strategies. The first approach consists of the identification of the gene networks that are activated upon exposure to two classical first-line AEDs (carbamazepine and valproate) as well as two newer first-line AEDs (lacosamide and levetiracetam) in glutamatergic and GABAergic neurons derived from induced pluripotent stem cells. In a cohort of 1382 patients with available exome sequencing data we will then estimate each patient's AED-network properties by mapping the individual's functional variants to the respective genes. The graph theoretical parameters of each individual's network will then be tested as predictors for AED response using machine learning approaches. The second approach integrates detailed clinical information and biomarkers such as raw EEG, MRI and exome data of the same cohort to similarly develop a decision support tool for predicting the AED with the highest likelihood of success. We will optimize the decision support tool by integrating both approaches, compare them to the individual strategies and identify the parameters ultimately needed for a reliable prediction of AED response. Subsequently, we will select 100 independent patients from an available database with information on treatment outcome, assess the predictive parameters (e.g. perform exome sequencing and EEG) and evaluate if the predicted best AED corresponds with the observed most effective drug. Based on these results we will prepare a prospective multicentre randomized controlled trial with industry support.

2. PROJECT CONSORTIUM

For each of the partners participating in the project, please fill in the following table.

2.1. COORDINATOR – PROJECT PARTNER 1

Last Name	Klein
First Name	Karl Martin
Gender	Male
Title	Dr. med., PhD
Institution	University of Calgary
Type of entity	<input checked="" type="checkbox"/> Academia (research teams working in universities, other higher education institutions or research institutes) <input checked="" type="checkbox"/> Clinical/public health research sector (research teams working in hospitals/public health and/or other health care settings and health organisations) <input type="checkbox"/> Private partner
Department	Departments of Clinical Neurosciences, Medical Genetics and Community Health Sciences, Hotchkiss Brain Institute & Alberta Children's Hospital Research Institute, Cumming School of Medicine, Foothills Medical Centre
Position	Associate Professor (from September 2018)
Address	1403 29 Street NW
Postal Code	T2N 2T9
City	Calgary
Country/Region	Canada, Alberta
Relevant funding organisation	Canadian Institutes of Health Research
Phone	+49 162 9534800
Fax	+49 69 6301 84466
E-mail	mail@kleinkm.de
Other information ¹	Letter with confirmation of appointment attached
Other personnel participating in the project (please provide last and first names and positions, 1 line per person)	

¹ Industry: Additional information (such as VAT number, turnover, balance sheet) might be requested by your national / regional agency. Please check therefore the "Guidelines for applicants". If no additional information is requested by your national / regional funding organisation, please write «none».

2.2. PROJECT PARTNER 2

Last Name	Colin
First Name	Josephson
Gender	Male
Title	MD MSc FRCP(C) CSCN (EEG)
Institution	University of Calgary
Type of entity	<input checked="" type="checkbox"/> Academia (research teams working in universities, other higher education institutions or research institutes) <input checked="" type="checkbox"/> Clinical/public health research sector (research teams working in hospitals/public health and/or other health care settings and health organisations) <input type="checkbox"/> Private partner
Department	Department of Clinical Neurosciences, O'Brien Institute for Public Health & Hotchkiss Brain Institute, Cumming School of Medicine, Foothills Medical Centre
Position	Assistant Professor
Address	1403 29 Street NW
Postal Code	T2N 2T9
City	Calgary
Country/Region	Canada, Alberta
Relevant funding organisation (if no funding is requested, please write "none") ¹	Canadian Institutes of Health Research
Phone	+1 403.944.8916
Fax	+1 403.283.2270
E-mail	cbjoseph@ucalgary.ca
Other information ²	None
Other personnel participating in the project (please provide last and first names and positions, 1 line per person)	Jordan Engbers, CEO of Desid Labs Inc. (SME)

¹ If no funding is requested, a signed statement has to be enclosed declaring in advance that this partner will run the project with its own resources.

² Industry: Additional information (such as VAT number, turnover, balance sheet) might be requested by your national / regional agency. Please check therefore the "Guidelines for applicants". If no additional information is requested by your national / regional funding organisation, please write «none».

2.3. PROJECT PARTNER 3

Last Name	Chiocchetti
First Name	Andreas G.
Gender	Male
Title	Dr. rer. nat.
Institution	Goethe University Frankfurt a. M., University Hospital
Type of entity	<input checked="" type="checkbox"/> Academia (research teams working in universities, other higher education institutions or research institutes) <input checked="" type="checkbox"/> Clinical/public health research sector (research teams working in hospitals/public health and/or other health care settings and health organisations) <input type="checkbox"/> Private partner
Department	Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
Position	Head Molecular Genetics Laboratory
Address	Deutschordenstr. 50
Postal Code	60528
City	Frankfurt a.M.
Country/Region	Germany
Relevant funding organisation (if no funding is requested, please write "none") ¹	Federal Ministry of Education and Research (BMBF)
Phone	+49 (0) 69 6301 6127
Fax	+49 (0) 69 6301 80426
E-mail	Andreas.Chiocchetti@kgu.de
Other information ²	None
Other personnel participating in the project (please provide last and first names and positions, 1 line per person)	Afsheen Yousaf MSc, Bio-informatician
	Denise Haslinger MSc, Molecular and Cellular Biologist

¹ If no funding is requested, a signed statement has to be enclosed declaring in advance that this partner will run the project with its own resources.

² Industry: Additional information (such as VAT number, turnover, balance sheet) might be requested by your national / regional agency. Please check therefore the "Guidelines for applicants". If no additional information is requested by your national / regional funding organisation, please write «none».

2.4. PROJECT PARTNER 4

Last Name	Rosenow
First Name	Felix
Gender	Male
Title	Prof. Dr. med., MHBA
Institution	Goethe University Frankfurt a. M., University Hospital
Type of entity	<input checked="" type="checkbox"/> Academia (research teams working in universities, other higher education institutions or research institutes) <input checked="" type="checkbox"/> Clinical/public health research sector (research teams working in hospitals/public health and/or other health care settings and health organisations) <input type="checkbox"/> Private partner
Department	Epilepsy Center Frankfurt Rhine-Main, Department of Neurology
Position	Head Epilepsy Center
Address	Schleusenweg 2-16
Postal Code	60528
City	Frankfurt a. M.
Country/Region	Germany
Relevant funding organisation (if no funding is requested, please write "none") ¹	Federal Ministry of Education and Research (BMBF)
Phone	+49 69 6301 7466
Fax	+49 69 6301 84466
E-mail	rosenow@med.uni-frankfurt.de
Other information ²	None
Other personnel participating in the project (please provide last and first names and positions, 1 line per person)	Dr. Philipp Reif, Head of the Epilepsy Genetics Group, Epilepsy Center Frankfurt Rhine-Main, Goethe University Frankfurt

¹ If no funding is requested, a signed statement has to be enclosed declaring in advance that this partner will run the project with its own resources.

² Industry: Additional information (such as VAT number, turnover, balance sheet) might be requested by your national / regional agency. Please check therefore the "Guidelines for applicants". If no additional information is requested by your national / regional funding organisation, please write «none».

2.5. PROJECT PARTNER 5

Last Name	Kälviäinen
First Name	Reetta
Gender	Female
Title	Prof. Dr.
Institution	University of Eastern Finland, Kuopio University Hospital
Type of entity	<input checked="" type="checkbox"/> Academia (research teams working in universities, other higher education institutions or research institutes) <input checked="" type="checkbox"/> Clinical/public health research sector (research teams working in hospitals/public health and/or other health care settings and health organisations) <input type="checkbox"/> Private partner
Department	Epilepsy Center/NeuroCenter
Position	Head Epilepsy Center
Address	P.O. Box 1627
Postal Code	70211
City	Kuopio
Country/Region	Finland
Relevant funding organisation (if no funding is requested, please write "none") ¹	Academy of Finland (AKA)
Phone	+35 8 40 5839249
Fax	+35 8 17 17 3031
E-mail	Reetta.Kalviainen@kuh.fi
Other information ²	None
Other personnel participating in the project (please provide last and first names and positions, 1 line per person)	Oskari Timonen, MSc, Bio-informatician
	Ritva Vanninen, Professor of Neuroradiology
	Esa Mervaala, Professor of Clinical Neurophysiology

¹ If no funding is requested, a signed statement has to be enclosed declaring in advance that this partner will run the project with its own resources.

² Industry: Additional information (such as VAT number, turnover, balance sheet) might be requested by your national / regional agency. Please check therefore the "Guidelines for applicants". If no additional information is requested by your national / regional funding organisation, please write «none».

2.6. PROJECT PARTNER 6

Last Name	Pandolfo
First Name	Massimo
Gender	Male
Title	Prof. Dr.
Institution	Université Libre de Bruxelles, Hôpital Erasme
Type of entity	<input checked="" type="checkbox"/> Academia (research teams working in universities, other higher education institutions or research institutes) <input checked="" type="checkbox"/> Clinical/public health research sector (research teams working in hospitals/public health and/or other health care settings and health organisations) <input type="checkbox"/> Private partner
Department	Department of Neurology
Position	Director of the Laboratory of Experimental Neurology
Address	808 Route de Lennik
Postal Code	1070
City	Brussels
Country/Region	Belgium
Relevant funding organisation (if no funding is requested, please write "none") ¹	Fund for Scientific Research (F.R.S.-FNRS)
Phone	+32 2 555 34 29
Fax	+32 2 555 41 21
E-mail	Massimo.Pandolfo@ulb.ac.be
Other information ²	None
Other personnel participating in the project (please provide last and first names and positions, 1 line per person)	Prof. Dr. Chantal Depondt, Hôpital Erasme, Université Libre de Bruxelles

¹ If no funding is requested, a signed statement has to be enclosed declaring in advance that this partner will run the project with its own resources.

² Industry: Additional information (such as VAT number, turnover, balance sheet) might be requested by your national / regional agency. Please check therefore the "Guidelines for applicants". If no additional information is requested by your national / regional funding organisation, please write «none».

2.7. PROJECT PARTNER 7

Only in case of inclusion of partners from underrepresented countries. These partners must be eligible research groups from the following funding organisations: Canada (FRQS, CIHR), Croatia (MSE), Estonia (ETAg), Germany (Saxony), Italy (Lombardy, FRRB), Romania (UEFISCDI), Spain (GN), Spain (CDTI), Turkey (TUBITAK).

None

PROJECT DESCRIPTION

3.1. PROPOSED WORK (MAX. 3 PAGES)

1. *Justify how the proposal fits in the scope of the call*

Our proposal combines highly innovative preclinical research with state of the art bio-informatics and ICT approaches for network and big data analysis, exploiting already existing exome data of 1382 patients. This work will provide insights into fundamental principles of antiepileptic drug response and will lead to the development of decision support tools allowing a rational individualised selection of antiepileptic drugs in epilepsy patients. The successful application of our research methods will not only demonstrate the feasibility of personalised medicine in epilepsy but can also be applied to different diseases, for example psychiatric disorders, in the future.

2. *Explain the Personalised Medicine dimension of the proposed work and its added value to the scientific question addressed in the proposal*

Epilepsy is one of the most frequent chronic neurological disorders and is characterised by recurrent seizures with a major impact on quality of life. It affects more than 70 million people worldwide of all age groups¹. Currently the primary therapy for epilepsy, i.e. antiepileptic drugs, are selected based on trial and error since there is considerable interindividual variation with regards to seizure outcome. Thus, there is an urgent need to predict the effect of a particular antiepileptic drug (AED) for each individual patient to increase therapy success and decrease costs. Decision support tools assisting the clinical decision for selection of the AED with the best chance of success in individual patients (personalised medicine) would significantly increase the individual's quality of life and revolutionise epilepsy treatment.

Our proposal aims at developing such decision support tools using two approaches. The first approach consists of the identification of the gene networks that are activated upon exposure to two classical first-line AEDs (carbamazepine and valproate) as well as two newer first-line AEDs (lacosamide and levetiracetam) in glutamatergic and GABAergic neurons derived from induced pluripotent stem cells. This will not only advance our understanding of the fundamental principles of antiepileptic drug response but will also allow to map functional variants of 1382 epilepsy patients with available exome sequencing data to the respective gene networks. The graph theoretical parameters of each individual's network will then be tested as predictors for AED response using machine learning approaches. The second approach will integrate detailed clinical information and biomarkers such as raw EEG, MRI and exome data of the same patient cohort to similarly develop a decision support tool for predicting the AED with the highest likelihood of success. Afterwards, an optimised version of the decision support tool will be developed by integrating both approaches. Subsequently, we will evaluate the decision support tool in 100 independent patients selected from an available database with information on treatment outcome and, finally, prepare a prospective multicentre randomised controlled trial with industry support evaluating the decision support tool.

We anticipate that our decision support tool will be able to inform doctors and patients about the antiepileptic drug with the highest likelihood of success. Based on this information doctors can appropriately advise patients about the available antiepileptic drugs and patients can make a rationale and informed decision.

3. *Background, present state of the art and preliminary results obtained by the consortium members*

Personalised medicine in epilepsy has already shown very promising results in monogenic epilepsies. In these epilepsies mutations in single genes are responsible for the phenotype and therapeutic approaches aiming at reversing the effect of the particular mutation are applied. Examples for this strategy are the mTOR inhibitor everolimus in tuberous sclerosis and the ketogenic diet in glucose transporter deficiency^{2,3}.

However, in the common epilepsies, which represent the majority of epilepsy, multiple genes or acquired lesions are responsible and, therefore, the strategies applied in monogenic epilepsies are not applicable to these patients. Nevertheless, there is strong evidence that genetic or environmental factors modify treatment effect and adverse drug reactions in patients with common epilepsies⁴. The strongest evidence exists for the HLA-B*1502 genotype which is associated with the development of Stevens-Johnson syndrome as an adverse drug reaction to carbamazepine in the Southeast Asian population⁵. So far, only a few genes with minor impact on treatment effect have been identified^{6–14}. The current evidence is insufficient to make meaningful predictions on an individual basis^{15,16} and the mentioned polymorphisms are not routinely tested before initiating AED therapy.

Our proposal will overcome the current lack of evidence by combining highly innovative bio-informatics network, big data and ICT approaches which outclass previous gene-based approaches. The project will result in a decision support tool for selection of the antiepileptic drug with the highest likelihood of success. Our research methods can be applied to other antiepileptic drugs and other diseases in the future.

4. Brief description of the working program including the objectives, the rationale and the methodology, highlighting the novelty, originality and feasibility of the project

Rationale: In contrast to previous studies, which have focussed on identifying individual genes being associated with treatment response, we intend to integrate the genetic information of each individual with the gene networks implicated in AED response. It has been shown that AEDs lead to widespread changes in gene expression^{17–21}. We therefore seek to define the molecular networks of four AEDs, carbamazepine (CBZ) and valproate (VPA), representing classic first-line AEDs, as well as levetiracetam (LEV) and lacosamide (LCM), representing newer first-line AEDs. The respective gene expression signatures have so far not been properly assessed in human neurons. Since alterations in cortical networks leading to epilepsy involve changes in excitatory glutamatergic neurons and inhibitory GABAergic neurons, these neuronal subtypes are likely to be differently affected by AEDs. For this reason, we plan to define the transcriptomic networks of the selected AEDs for both subtypes, differentiated from induced pluripotent stem cells (iPSC) of healthy individuals, which currently is the best in-vitro model for neuronal processes. Next, we will model the network vulnerability of affected individuals as estimated based on the potential effect of genetic variants on the AED-co-regulated gene network. Using machine learning techniques, we aim to investigate these novel markers as predictors for treatment response. This approach will considerably improve power compared to gene-based approaches and more closely reflects the dynamic regulatory effects in the brain. In parallel, we will combine detailed clinical information, biomarkers and exome sequencing data to develop clinical decision support tools for a rational choice of AED in the individual patient. Finally, we aim to compare and integrate the developed algorithms to identify the approach with the highest reliability and clinical usability. The final algorithm will be explored in an independent cohort.

Objectives and methodology:

AIM 1 (Module 1A): Delineating the gene networks implicated in CBZ, VPA, LCM and LEV response

The integration of the co-regulatory effects of genetic variants on the gene expression network level is of utmost importance for predicting treatment response to different AEDs. We therefore aim to (1) identify the differentially expressed genes and underlying co-regulatory gene-modules (sub-networks) in iPSC-derived GABAergic and glutamatergic neurons exposed to the AEDs CBZ, VPA, LCM and LEV and (2) use this network data to define the normative gene networks and their properties implicated in the exposure of both neuronal subtypes to each of these AEDs.

AIM 2 (Modules 1B, 2A): Translate the individuals' genetic burden into predictors for response for CBZ, VPA, LCM and LEV

To pave the way towards personalised medicine treatment approaches in common epilepsies it is of high importance to identify markers that are predictive for treatment response to the different AEDs. Therefore, we aim to (1) harmonise clinical data and categorise treatment response to the

different AEDs in an available cohort of 1382 patients; (2) define the patients' individual AED-response network properties (aim 1) using available exome sequencing data of each patient and (3) identify subgroups of patients based on the individuals' AED-network parameters to test them for correlation with clinical phenotypes and AED response.

AIM 3 (Module 2A, 2B): Development of decision support tools for AED choice in epilepsy patients

To overcome the current trial and error approach when treating epilepsy patients with AEDs we will develop a decision support tool for AED choice between CBZ, VPA, LCM and LEV. Three different versions will be developed based on different datasets and analysis methods: (A) Decision support tool based on the AED implicated gene network parameters, (B) Decision support tool based on clinical phenotypic information and biomarkers such as EEG, MRI and exome data, (C) decision support tool combining (A) and (B). A data repository will be set up to provide inclusion and harmonization of this rich dataset to be made available for future analyses for other research groups and to integrate data on additional AEDs. Furthermore, web-based, smartphone, and tablet applications will be created to facilitate uptake.

AIM 4 (Module 1B): Evaluation of the decision support tools in an independent cohort

The confirmation of the utility of the decision support tools in an independent cohort will provide strong evidence for the generalisability of the algorithms and the applicability in the clinical setting. Consequently, we will perform exome sequencing and apply the decision support tools in 100 not previously included patients who showed response to one of the examined drugs in the past but failed at least one other. We will compare the different versions of the decision support tools regarding their ability to correctly predict the effective AED. A prospective, multicentre randomised controlled trial with industry support will be prepared using the best decision support tool to pave the way for application of this personalised medicine approach in clinical practice.

5. Describe of the unmet medical and patient need that is addressed by the proposed work and the potential health impact that the results of your proposed work will have.

It is currently impossible to predict the effect of the different AEDs in individual patients. Using the current trial and error approach less than one in two patients become seizure free with the first chosen AED²², resulting in increased costs and burden for health care providers, society and most importantly for the patients due to injuries, death, social stigma as well as vocational and driving restrictions. The development of decision support tools that allow choosing the AED with the highest likelihood of success for the individual patient would revolutionise AED treatment. Shortening the period until seizure freedom is reached will considerably reduce the burden for the patients resulting in higher patient satisfaction, which will further improve seizure outcome due to better drug adherence and decrease costs to care providers and society.

3.2. PRELIMINARY RESULTS (MAX. 2 PAGES)

Partner 6 has extensive experience in culturing and differentiating human iPS cells into neurons. In published work, *Partner 6* has generated and characterized cortical neurons, both glutamatergic and GABAergic, from control iPS cells and iPS cells from patients with Friedreich ataxia. Characterization of neurons included morphology, biochemistry, and excitable properties at the network and single cell level. These studies allowed to identify a specific cellular phenotype in neurons from Friedreich ataxia patients and to characterize its response to potential therapeutics^{23–25}. *Partner 6* also used human neurospheres derived from iPS cells from control individuals to characterize the subcellular localization of the DEPDC5 protein, mutations of which are a prominent cause of focal epilepsy²⁶.

Partner 3 has established a pipeline to analyse the transcriptomic signatures of neuronal cells (Figure 1), which includes the identification and characterization of gene-networks, the underlying graphs and subgraphs, and to characterise the graph-theoretical properties of each gene and the respective co-regulations. This pipeline has previously been implemented to identify, that genes with rare mutations are enriched among highly connected nodes of the gene networks activated during in-vitro neuronal development. Furthermore, *Partner 3* has developed a genome-wide analysis pipeline integrating whole brain expression data to map the genetic aetiology of a disease to the developmental and regional signatures of neural development (Prepublished on BioRxiv²⁷). These available pipelines will be the basis to identify AED- associated gene networks and expanded to characterise the impact of an individual's genetic make-up on the normative graph theoretical properties.

Partners 4, 5 and 6 have contributed 1382 samples of patients with epilepsy for exome sequencing to the Epi25 collaborative (table 1). The patients have already been carefully and uniformly phenotyped regarding their epilepsy within the Epi25 project. Exome sequencing data for all 1382 sample has been returned to *Partners 4, 5 and 6* and is available for analysis within this proposal. Detailed phenotypic data for antiepileptic drug outcome is already available for the patients included by *Partner 6*. Ethics approval for pharmacogenetic studies is in place at all sites and all 1382 patients have provided written informed consent. Consent to deposition of sequencing and clinical data in a data repository is available for 1240 samples. This phenotypic and genetic data on 1382 epilepsy patients will be fundamental for work packages 2 and 3.

The existing database of the Comprehensive Epilepsy Program (CEP) at *Partner 1 and 2's* institution includes drug dosage and seizure frequency at all clinical visits for almost 6000 patients. This database provides the basis for selected recruitment of highly informative patients for the confirmation analysis of the decision support tool in work package 4. Approval for analysing raw EEG and MRI data has already been granted at *Partner 1, 2 and 5's* institution. *Partner 5* has already collected epilepsy type, MRI, EEG, cognitive and TMS data in the single center 'biomarkers of epilepsy' study in a Redcap registry and continues prospectively to collect detailed information of all the clinic visits of all their patients; currently altogether 2500.

The CEP registry contains identifiable data and is maintained in databases hosted on secure servers within the Health Knowledge Hub at the University of Calgary in compliance with institution privacy regulations and processes. The Health Knowledge Hub is a secure server zone that can only be accessed via strictly controlled internal networks. Personal Health Numbers are used to link individual MRI (in DICOM format) and EEG (as .eeg files converted to MATLAB arrays) data to the CEP registry so that high-dimensional biological, demographic, and clinical data can be used to test the prediction model. Currently, we have linked 180 MRI studies to CEP patients and are featurising the data for predictive purposes. Processes are now being created for extraction and storage of EEG files from the Calgary EEG Laboratory on secure servers. These studies are already available so analyses will start almost immediately after standard operating procedures are created. Currently, there are 821 patients on carbamazepine, 587 on valproic acid, 880 on levetiracetam, and 44 on lacosamide indicating that the aim of 25 patients per drug can be well achieved.

Table 1. Samples with epilepsy and available exome sequencing data

Site	Number	Status
Germany - Partner 4	259	exome sequencing done, data received
Finland - Partner 5	736	exome sequencing done, data received
Belgium - Partner 6	387	exome sequencing done, data received
Total	1382	

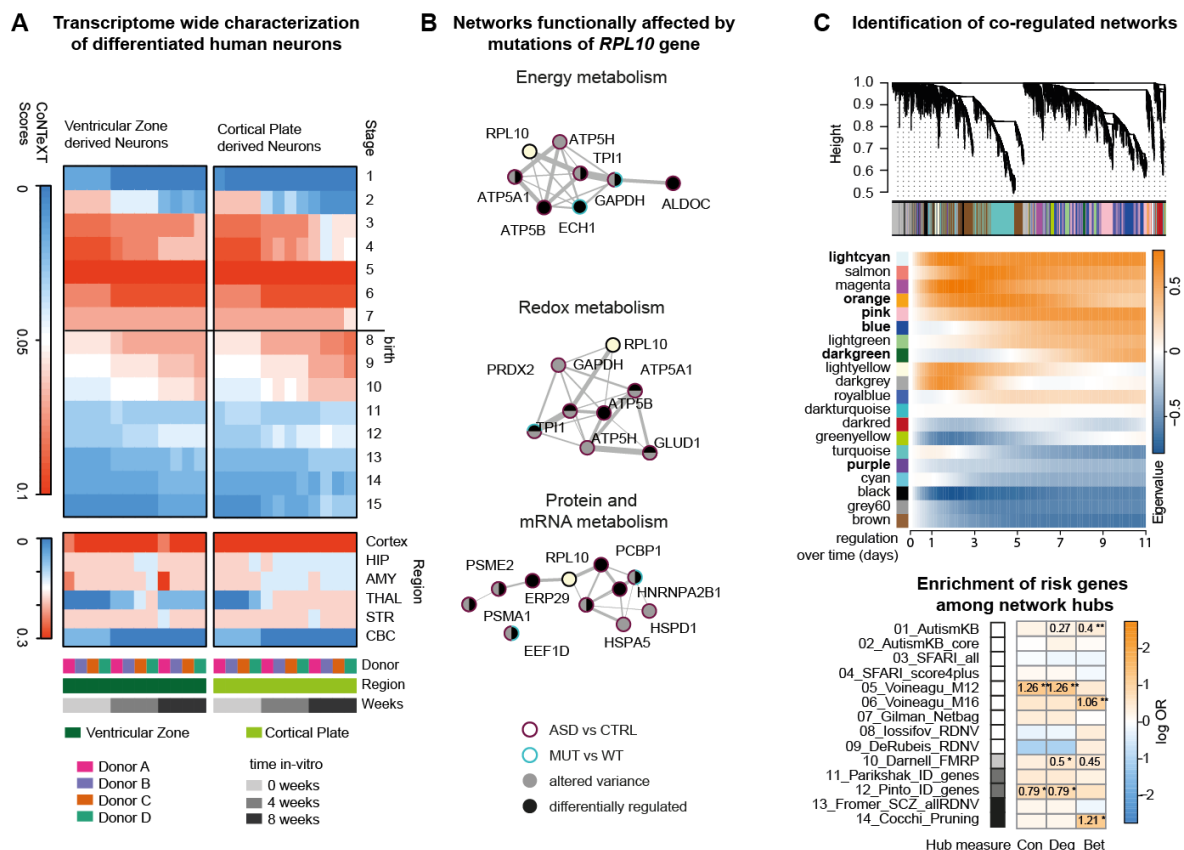
2. Preliminary data

Figure 1: Bioinformatic approaches used within project 1+2 **A)** Characterization of neurons based on whole genome transcriptome (method used in Chiocchetti et al. 2016) using the CoNTEXT algorithm (Stein, de la Torre et al. 2014) evaluates transcriptomic signatures of neurons using machine learning algorithms and predicts brain region and developmental stage based on in-vivo human datasets. High CoNTEXT scores thus indicate the Stage and Region a sample most likely belongs to. **B)** Identification of network altered by mutations of the ribosomal protein RPL10 (Chiocchetti et al. 2014). Using a whole proteome approach we identified three vulnerable networks in individuals with Autism Spectrum Disorder (ASD) and individuals with RPL10 mutations associated with ASD (Chiocchetti et al. 2014). **C)** Whole transcriptome network analysis and characterization. We identified co-regulated modules activated or inhibited during neuronal differentiation and could show that hub genes are enriched (corr.p.val < 0.05 marked by *) for genes hit by genetic variants associated with ASD, Intellectual disability (ID) or schizophrenia (SCZ). Hub genes were defined by network measures for quality of connections (Connectivity, Con.), quantity of connections (Degree, Deg.) and Information flow through a gene (Betweenness, Bet., Chiocchetti et al. 2016)

3.3. CHANGES IN THE PROPOSAL BETWEEN THE PRE- AND FULL PROPOSALS (MAX 1 PAGE)

No changes in the composition of the consortium and the overall work plan were made in the full proposal. *Partners 1* and *2* are based in Canada, which is an underrepresented country, and were already part of the pre-proposal. Funding for the German *Partners 3* and *4* was adjusted to fulfil the requirements of the Federal Ministry of Education and Research (BMBF) without changing the work plan presented in the pre-proposal. *Partners 3* and *4* will cover 20% of the cost for personnel from local available budget. Furthermore, an alternative partner was considered for RNA sequencing to reduce costs. To compensate a slight increase in cost for data analysis, *Partner 2* will cover the cost for open-access publications from local available budget.

We would like to thank the reviewers for the positive comments and helpful suggestions. Based on these, the following changes were made in the full proposal:

- The expertise of *Partners 4, 5* and *6* was pointed out more clearly. *Partners 4, 5* and *6* are highly skilled clinical epileptologists whose experience will be required for evaluating treatment response in the already exome sequenced patients as part of the proposal. They will also be paramount for planning the randomised controlled follow-up study and acquire industry support. These partners have extensive experience in planning and conducting clinical trials in epilepsy and are successfully coordinating and conducting multinational research projects (e.g. EpimiRNA (FP7) and EPICURE (FP6), EpiXchange-Initiative consortium).
- It was emphasised that the existing ethics approvals at all sites allow inclusion of all Epi25 patients in pharmacogenetics research and informed consent covering this is available for all patients. 977 of the 995 patients of *Partner 4* and *5* have also consented to be re-contacted. The remaining 387 patients of *Partner 6* do not need to be re-phenotyped as AED outcome data is already available.
- We have carefully discussed including gabapentinoids such as gabapentin or pregabalin. Although widely used for pain treatment, gabapentinoids are rarely used for epilepsy treatment in the countries involved. In addition, pregabalin is only approved as an add-on treatment in epilepsy and can, therefore, not be applied in newly diagnosed patients. Therefore, it is unlikely that a sufficient number of patients in our cohort will have been exposed to gabapentinoids. For these reasons, we have not included gabapentinoids in this proposal but are happy to investigate these in a follow-up study.
- We have pointed out in the proposal, particularly in section 3.13, that there are no regulatory or ethical obstacles for conducting the proposed research.
- We have removed the existing inconsistencies regarding the involvements of the partners in the different work packages.
- We have added a sustainability plan for long-term storage of the data in a data repository after the end of the project. We plan to take advantage of the data sharing facilities within the 'international epilepsy data ecosystem' that will be implemented by the EpiXchange initiative consortium. *Partner 4* is a member of the organizing committee of EpiXchange 2018 (<http://www.epixchange2018>).
- We are confident that *Partner 1*'s request for consumables is sufficient for DNA extraction of 100 samples and have, therefore, not changed the budget. Funding for the exome sequencing is included in 'other costs' as it will be done at a core facility at the University of Calgary.
- The RNA extraction from iPSC cells will be done by *Partner 6*. Therefore, *Partner 3* does not require consumables as a bio-informatics department. For RNA sequencing we decided to collaborate with the West German Genome Center in Bonn/Köln/Düsseldorf at an academic level which markedly reduces costs for RNASeq analysis.
- *Partner 1* will be moving to the University of Calgary before the start of the project. Dr. Philipp Reif will take over the lead of the Epilepsy Genetics Research Group at *Partner 4*'s institution but Prof. Felix Rosenow will be the principal investigator. As requested, curricula vitae of all principal investigators are attached below.

3.4. WORK PLAN INCLUDING REFERENCES (MAX. 8 PAGES)

AIMS

1. Delineating the gene networks implicated in CBZ, VPA, LCM and LEV response (Module 1A)
2. Translate the individuals' genetic burden into predictors for response for CBZ, VPA, LCM and LEV (Modules 1B, 2A)
3. Development of decision support tools for AED choice in epilepsy patients (Module 2A, 2B)
4. Evaluation of the decision support tools in an independent cohort (Module 1B)

METHODOLOGY WITH WORK PACKAGES, ROLE OF EACH PARTICIPANT AND TIMELINE

Work Package 1 with Aim 1: Delineating the altered gene networks for CBZ, VPA, LCM and LEV [Partners 3 and 6]

Generation of induced pluripotent stem cells (iPSC) and exposure to antiepileptic drugs (Partner 6; month 1-9)

Partner 6 will generate glutamatergic and GABAergic human neurons from two control induced pluripotent stem cell (iPSC) lines (1 male, 1 female) in two biological replicates (subclones) each. Glutamatergic neurons will be generated by differentiating human iPSCs into neurons in the absence of exogenous morphogens. This results in early Tuj1/MAP2 neuronal cells in relatively high purity ($\pm 5\%$ astrocytes), whose transcription profile resembles that of fetal brain²⁸. These neurons express forebrain cortical markers, corresponding to glutamatergic neurons in various cortical layers²⁹. In these cultures, a small proportion of GABAergic cells are found. Specific differentiation protocols allow instead to obtain highly enriched cultures for GABAergic neurons³⁰. After obtaining neural precursors, treatment with purmorphamine confers medial ganglionic eminence (MGE)-like fate. MGE-like progenitors are then induced to differentiate into GABAergic neurons on Matrigel-coated coverslips in DMEM/F12, 1× non-essential amino acids, and 1× N2 supplement, containing 1 μ M cAMP, 10 ng/ml BDNF, 10 ng/ml glial GDN, 10 ng/ml IGF-1 for 4–6 weeks. The mature neuronal cells will be exposed to the antiepileptic drugs CBZ, VPA, LCM and LEV. mRNA will be extracted from exposed and non-exposed cells from each cell line using commercially available Kits (Qiagen) in order to quantify differential AED-dependent mRNA expression.

RNA sequencing (Partner 3; month 7-15)

Partner 3 will then perform quality-checking using the Agilent Bioanalyzer, followed by highly sensitive RNA sequencing at the West German Genome Center in Bonn/Köln/Düsseldorf. Libraries will be prepared using the TruSeq mRNA stranded kit which includes Ribo-Zero ribosomal RNA reduction at a read depth of 50M reads paired-end with a length of 2x50bp. Reads will be processed and aligned using cutadapt³¹ and bowtie2³² based on the standard parameters. In contrast to microarrays, this method allows the detection of low abundant transcripts, differentiation between alternative splicing isoforms or 3'UTRs with high accuracy and characterization of long non-coding RNAs.

Network analysis (Partner 3; month 13-21)

Partner 3 will identify the implicated molecular networks (co-regulated gene-modules), adapting weighted gene co-expression network analysis (WGCNA³³) paralleled by classical differential gene-expression analysis using the DESeq2 pipeline³⁴. The networks will be refined by integrating existing post-mortem in-situ gene-expression data of the human brain and human cortical single cell studies. Subsequently, the regulatory hub-genes for each of the defined gene-modules will be identified based on node centrality measures within all respective gene modules. Finally, the normative graph-theoretical parameters of the gene networks implicated in response to CBZ, VPA, LCM and LEV will be identified and characterised in glutamatergic and GABAergic neurons respectively. In parallel, to understand the underlying biological mechanisms, each module will be tested for association with specific GO-term and KEGG pathways using the GO-Elite software

package. All graph theoretical approaches will be implemented in R using the igraph package and in-house scripts.

Work Package 2 with Aim 2: Establishing a correlation between the genetic burden in the altered gene networks and treatment response for CBZ, VPA, LCM and LEV [Partners 3-6]

AED outcome phenotyping (Partners 4, 5 and 6; month 1-18)

Partners 4, 5 and 6 have contributed 1382 samples of patients with epilepsy for exome sequencing to the Epi25 collaborative (table 1). The Epi25 collaborative is supported by the United States National Human Genome Research Institute (NHGRI) and aims to understand the inherited components of epilepsy (<http://epi-25.org>). All contributed samples have already been exome sequenced and the exome sequencing data (VCF and BAM files) has been returned to *Partners 4, 5 and 6* for use in own research projects. Publication of results from own research projects using Epi25 data is embargoed until the publication of the collaborative paper, which is expected to be published in 2018 or early 2019. As the analysis within this proposal will not be completed before 2021, the publication embargo will be lifted well beforehand.

The Epi25 collaborative does not focus on pharmacogenetic questions. Therefore, the clinical data obtained within the Epi25 project does not include treatment outcome. However, *Partners 4, 5 and 6* have detailed patients' records including data on treatment response to different AEDs. Seizure outcome to the four selected AEDs will be analysed, harmonised, categorised and databased for all patients within the proposed project. The outcome phenotyping to the different AEDs will be done using well-established case report forms (CRFs) developed within the EpiPGX consortium (<http://www.epipgx.eu>). Dr. Chantal Depondt (Professor in the epilepsy unit at *Partner 6's* institution) was responsible for the assessment of AED outcome and adverse drug reactions within the EpiPGX consortium. Due to her involvement in the EpiPGX consortium her Epi25 samples have already been phenotyped using the EpiPGX CRFs regarding AED outcome and can be readily analysed within the proposed project. *Partners 4 and 5* will perform the AED outcome phenotyping within the proposed project using the same EpiPGX CRFs. If required, patients will be re-contacted. The CRFs will be securely hosted online using the Redcap database by the clinical research unit at *Partner 1 and 2's* institution. The focus of this project will be the treatment response. However, data on adverse drug reactions will be categorised and databased as well and be available for future analyses.

All sampled patients have already been phenotyped regarding their epilepsy within the Epi25 collaborative. Therefore, detailed harmonised information on the type of epilepsy, seizure types, seizure frequency, age at onset, sex as well as results of investigations including EEG and MRI is readily available for analysis within work package 3. Additional parameters such as Epilepsy Specific Comorbidity Index³⁵, AED polytherapy and defined daily dose of AEDs will be extracted from the medical records. *Partners 4 and 6* will obtain IRB approval for including raw EEG and MRI data into the analysis. IRB approval for including raw EEG and MRI data is already in place at *Partner 5's* institution. If required by the IRB, informative patients with available exome data will be re-contacted and written informed consent for including raw EEG and MRI data will be obtained. Subsequently, raw EEG and MRI data will be provided for analysis within work package 3. As an EEG is routinely done during clinical workup we expect that EEG data will be available in virtually all patients with available exome data. We estimate that MRI data will be readily available in about 60% of patients and an additional 20% can be obtained from external radiology clinics.

Cluster analysis (Partner 3; month 19-24)

Partner 3 will model the individuals' vulnerability of the AED response networks using the available exome sequencing data of the 1382 samples. Identified functional variants will be weighted based on the predicted impact (Annovar) as well as the gene's sensitivity to mutations (RVIS score) and mapped onto the normative networks associated with each AED response in GABAergic and glutamatergic neurons as identified in work package 1. For each individual the alteration of graph-theoretical parameters such as centrality, information flow, or density measures will be

calculated and used as potential markers for AED response. We will define several parameters for network vulnerability based on Barabasi's network models in biology³⁶. Each gene in a specific network can be ranked based on its centrality measures, i.e. the number (Centrality) and intensity of connections to other genes (Connectivity) or the amount of information flowing through the gene (Betweenness). Based on this we assume that loss of function mutations of genes with high centrality ranks make a network less stable. At the network level we can define overall graph properties based on the connections between the genes (vertices) and define the density and information content of a network. Again, we assume that loss of a node (gene) alters the overall network structure and stability. We and others have shown that the transcriptomic signatures of biological responses can be grouped into ~30 co-regulated modules (sub-graphs). Here, we aim to calculate node and network properties for each of the identified AED modules (~4 x 30) for each individual.

These personalised network properties will be fuelled into unsupervised machine-learning-based clustering approaches to identify subgroups within the 1382 patients. We will therefore first calculate the Euclidean distances between each individual and subsequently implement self-organizing maps (SOMs). Subclusters will finally be identified using partition around methods (PAM) and evaluated based on silhouette measures and respective plots. As an alternative approach we will use random-forest-based proximity scores as distance measures in combination with PAM clustering which allows to also identify the most informative variables. Expertise in machine learning approaches will be exchanged with *Partner 2*.

Subsequently, *Partner 3* will test for associations of the identified strata with treatment response to the different AEDs.

At this stage, no information is available on cluster size or characteristics. However, assuming four equally sized clusters, an alpha error of 0.05 and a power of 80%, significant small effect sizes of $f > 0.10$ can be detected when implementing ANOVA including fixed and main effects and a nominator $df=7$ using the total sample of $N=1382$ individuals.

Work Package 3 with Aim 3: Development of a decision support tool for AED choice [Partners 1, 2, 3, 6]

Data homogenisation (Partners 1, 2 and 6; month 1-18)

All partners will use the same standardised CRFs that have been developed by the EpiPGX consortium when assessing treatment response and adverse effects to the selected antiepileptic drugs from patient files or during direct interviews. The epilepsy phenotype has already been obtained using a standardised CRF within the Epi25 collaborative. Randomly selected data entries by *Partners 4, 5 and 6* will be reviewed by *Partners 1, 2 and 6* for quality control. *Partner 6* will not review their own samples. This process will ensure that homogeneous data is available for all 1382 samples.

The exome data is available in VCF format provided by the Broad institute for all samples. Variants deviating from the hg19 consensus sequence were called using the Genome Analysis Toolkit (GATK). We do not expect any issues when combining the data as the calling was performed using the same parameters for all samples at the same site (Broad institute). However, should any issues arise when combining the data for the different samples we will revert to the BAM files and perform the calling for the whole cohort again using the high-performance servers at the University of Frankfurt.

Additional steps are required when integrating raw MRI and raw EEG into the analysis. The DICOM format is standard for MRI data and readily available at all sites. On the other hand, EEG data is stored in different formats depending on the manufacturer of the EEG device. However, the EDF (European Data Format) specification is emerging as a common standard and manufacturers typically offer interfaces to export the EEG data into EDF format. Therefore, EEG data will be converted to EDF format before analysis. When required, .eeg files will be converted to EDF format to homogenise records.

Big data analysis (Partner 2; month 19-24)

Partner 2 will perform a big data analysis using classification-based machine learning algorithms to identify predictors for treatment response to CBZ, VPA, LCM and LEV. The analysis will include detailed clinical information collected by *partners 4, 5* and *6* as well as biomarker and exome data. The clinical information will include age of onset, sex, epilepsy syndrome, drug response, seizure type, monthly seizure frequency, number of AEDs, daily dose of AEDs, the Epilepsy Specific Comorbidity Index, results of diagnostic tests and concomitant diseases. The raw EEG and MRI data as well as additional biomarkers (cognitive, neuropsychiatric, TMS, TMS-EEG, blood-based biomarkers) identified in the ongoing “biomarker in epilepsy” project of *partner 5* will be included. Comparing patients with and without available raw EEG and MRI data, we will assess the additional effect of this data on the prediction.

To optimise supervised machine learning, the component data will need to be featurised. We will explore the utility of converting raw EEG signal into measures of entropy, fractal dimension, Hjorth parameters, Hurst exponent, Lyapunov exponent, absolute and relative EEG power, power ratio in different frequency bands, and wavelet transformations. Raw signal data from MRI will be converted to reported raw MRI features including apparent diffusion coefficient parameter maps, regional brain volumes, voxel-based morphometry, cortical thickness, grey-white matter ratio, and fractal analysis.

After compiling patient features, we will experiment with different supervised machine learning algorithms to determine which is most effective, including: support vector machines, random forest ensembles, Naïve Bayes networks, and Gaussian processes, moving to other methods if necessary. While these machine learning algorithms often perform well, they require features to be determined *a priori*. Representation learning algorithms, such as deep neural networks, can automatically discover predictive features in raw and/or high-dimensional data. Therefore, we will also train convolutional neural networks to classify patients based on their genetic networks, MRI images, and EEG recordings (either raw traces, wavelet transforms, or bivariate correlation features). These classifiers will then be combined with feature-based classifiers into a hybrid multiple classifier system to improve overall predictive performance.

Performance of the predictive models will be compared using Area Under the Receiver Operator Characteristic curve (AUROC), F1 score, and Brier Score. We will incorporate k-fold cross-validation for model validation.

Decision support tool development (Partners 2 and 3; month 25-30)

Partners 2 and *3* will develop three different decision support tools to predict the antiepileptic drug with the highest likelihood of success in an individual patient.

Version A: This version will be based on the individual's specific antiepileptic drug network parameters. Machine learning algorithms such as random forests or deep learning networks will be implemented to train predictors for antiepileptic drug response using the individual's specific antiepileptic drug network parameters. The model will be further improved by including variants in genes within literature-based pathways associated with epilepsy, such as Glutamergic and GABAergic signalling, in the classifier. *Version B:* This version will be based on the big data analysis performed in work package 3. Briefly, these decision support tools will encompass four separate models (one for each of CBZ, VPA, LEV, and LCM) created through supervised techniques. Here, patient outcome (6-month and 1-year seizure freedom) is known in advance of model training and testing, the exposure will be one of the classical (CBZ and VPA) or newer (LEV and LCM) AEDs, and aforementioned phenotypic features will include clinical, EEG, MRI, and exome data.

Version C: Both strategies will be combined in Version C to achieve the optimal prediction.

Development of web-based app (Partner 2; month 31-36)

The major aim of the consortium is to establish the decision support-tool in clinical practice as soon as possible to improve patient care. As this process will strongly depend on industry support, for example for the planned randomised controlled study, the consortium will prioritise

patenting of the developed approaches to increase exploitability. However, the algorithms will be made available for free non-commercial use whenever possible.

To facilitate uptake of the decision support tool, *Partner 2* will develop a web-based application that allows prediction of the AED with the best chance of success after entering the required clinical information and biomarker data as well as uploading the individual's exome, EEG and MRI data (VCF, DICOM and EDF files). Usage of this web-based application will be restricted to non-commercial purposes.

Generation of data repository (Partner 2; month 31-36)

The proposed project will focus on treatment response, but side effects will be documented as well and can be addressed in future studies by consortium members or other research groups. To facilitate follow-up studies and the inclusion of the generated data in large collaborative studies *Partner 2* will setup a data repository that will be integrated within the 'epilepsy data ecosystem' implemented by the EpiXchange initiative before the end of this proposal. The data repository will include the phenotypic information on treatment outcome and epilepsy, biomarker data as well as exome, raw EEG and raw MRI data. Access to other research groups will be granted upon request.

Work Package 4 with Aim 4: Evaluation of the decision support tools in an independent cohort [Partners 1, 2, 4, 5, 6]

Patient selection and recruitment (Partners 1 and 2; month 1-24)

The Comprehensive Epilepsy Program in Calgary maintains a database that includes detailed information on every clinical visit of almost 6000 patients. Patients are asked to provide consent to be contacted for future research studies at their first visit to the CEP clinics. To date, a total of 4494 patients (75%) have expressed their interest and provided consent. The database is hosted by the Clinical Research Unit at *Partner 1* and *2*'s institution and includes information on antiepileptic drug dosage and seizure frequency. Based on this information, the effect of the different AEDs on seizure frequency can be objectively quantified.

Partners 1 and *2* will query this database to identify those patients who responded to either CBZ, VPA, LCM or LEV but failed at least one other of these drugs. For each drug 25 patients with a positive response will be recruited. Priority will be given to those patients who showed an excellent response to one drug (seizure freedom) but failed all as many as possible of the other selected drugs. As patients with outcome data to all 4 selected drugs will be rare, we stipulate as the minimum requirement for inclusion that outcome data on two antiepileptic drugs is available with response to one and no response to the other drug. As an EEG is routinely done in epilepsy patients raw EEG data will be available for all patients. Patients with available raw MRI data will be prioritised as well.

The selected patients will be contacted and asked for participation in the study. Ethics for big data analysis including genetic as well as raw EEG and MRI data has already been approved by the local Institutional Review Board in Calgary. After providing written informed consent the phenotypic data of these patients will be obtained and documented using the standardised CRFs of the EpiPGX consortium and Epi25 collaborative. In addition, peripheral blood samples of the patients will be obtained, and genomic DNA will be extracted using standard protocols. Integration of raw EEG and MRI data is already established in Calgary.

Exome sequencing (Partner 1; month 25-30)

Exome sequencing will be performed at the Centre for Health Genomics and Informatics (core facility, Alberta Children's Hospital Research Institute, University of Calgary) using genomic DNA of the 100 selected patients (25 for each selected antiepileptic drug). Sequencing reads will be aligned to the reference genome and variants will be called using the Genome Analysis Toolkit (GATK).

Decision-support tool evaluation (Partners 1 and 2; month 31-36)

The different versions A, B and C of the decision support tool will be used to calculate the likelihood of success for the selected AEDs in each of the 100 patients based on the phenotypic information, exome sequencing data, available biomarker data as well as raw EEG and MRI data. Subsequently, we will calculate the correlation between the predicted ranking of the antiepileptic drugs by the different versions of the decision support tools and the observed ranking in the individual patient. The decision support tool offering the best prediction will be selected.

Preparation of a multicentre randomised controlled trial (Partners 1, 4, 5 and 6; month 31-36)

To implement the precision support tool in clinical practice it will be required to show the beneficial effect in a randomised controlled trial. The implementation and conduction of a multicentre randomised controlled study is beyond the scope of this application. However, *Partners 1, 4, 5 and 6* will design and prepare such a prospective multicentre randomised controlled trial within this proposal based on the developed decision support tool and the information on effect size. The study will randomise the probands to either standard care with trial-and-error-based selection of antiepileptic drugs or personalised medicine treatment using the decision support tool. Primary outcome parameter will be the time until 6 months seizure freedom is reached. *Partners 1, 4, 5 and 6* will also acquire industry support so that the trial can be run as a follow-up study.

PROJECT COORDINATION AND MANAGEMENT

Partner 1, the coordinator, will be responsible for management, communication with ERA PerMed and stakeholders as well as other external requests. He will be supported by *Partners 2-6*, who are responsible for communication with their national funding agencies. The steering committee will consist of all partners of the proposal and decide about requests for access to the data repository.

A multinational advisory committee will provide advice regarding research program, ethics and good governance. The advisory committee will meet every six months either associated with the yearly project meetings or via telephone conference. The advisory committee will consist of one patient representative from each participating country (Belgium, Canada, Finland, Germany) and three external researchers.

Yearly project meetings will be held to facilitate the scientific exchange and coordination of research projects. Two of these will be held in Europe and one in Canada. Stakeholders and patient representatives will be invited to these project meetings to ensure that the research program is well aligned with patient needs. Their suggestions will be incorporated in the research program whenever possible.

The consortium will pay particular attention to an even gender distribution of research personnel and the advisory board. In addition, part-time positions will be offered to facilitate compatibility of family and research.

INNOVATION AND ADDED VALUE OF THE PROPOSED SOLUTIONS TO ADDRESS A MEDICAL NEED COMPARED TO EXISTING ONES

Antiepileptic drugs are the primary treatment of epilepsy. Although a large number of AEDs are available (~25 approved AEDs), it is currently not possible to predict the efficacy of the different AEDs in an individual patient. Epilepsy treatment, therefore, represents a trial-and-error approach of a number of AEDs until seizure freedom is reached. Using the current trial-and-error approach less than one in two patients become seizure free with the first chosen AED²² resulting in increased costs and burden for health care providers, society and most importantly for the patients due to injuries, death, social stigma as well as vocational and driving restrictions while other drugs are being tried. A decision support tool will allow selecting the antiepileptic drug with the highest chance of success. Our combination of highly innovative preclinical research with state of the art bio-informatic and ICT approaches for network and big data analysis incorporating

already existing exome data of 1382 patients will not only provide insights into fundamental principles of antiepileptic drug response but will also result in the development of a decision support tool incorporating phenotypic information on the epilepsy, biomarkers, genetic data and results of diagnostic tests. Establishing such a decision support tool in clinical care will revolutionise epilepsy treatment by introducing personalised medicine to decrease the time until patients become seizure free, increase quality of life and decrease costs for healthcare providers. The successful application of our research methods will demonstrate that personalised medicine is feasible in complex diseases paving the way for further discoveries in other diseases in the future.

RISK ASSESSMENT

The risk for the overall structure of the consortium is low, as all partners involved in RAISE-GENIC have a history of successful collaboration. Furthermore, *Partner 1's* participation in multiple European consortia including many of the other partners before moving to Canada will ensure a strong transatlantic collaboration. We are confident that the strong collaborative setup of this consortium will be able to deal with any unanticipated risks.

We consider the risk that the start of a work package is delayed due to outstanding results from another work package to be low as we have allocated sufficient time for completion. However, should delays occur the next work package will prioritise the parts of the research that can be started without the results from the previous work package.

It is expected that slow recruitment for positions within the proposal is unlikely to occur. The participating centres are highly competitive and can select from a large number of applications. We will, however, make sure that positions are advertised as soon as possible after the funding decision is made to allow sufficient time for recruitment.

The infrastructure for conduction of the research is in place at all sites. There is a low risk of equipment failure as tasks requiring expensive equipment are subcontracted to SMEs or core facilities. The risk for breakdown of the database at *Partner 1 and 2's* institution is low. However, regular and frequent backup strategies will be in place to avoid data loss. In the unexpected event of database downtime, it will be possible to use paper CRFs for temporary data entry.

There is no risk of failed recruitment in work packages 2 and 3 as the included 1382 patients have already been recruited with appropriate consent for conducting the pharmacogenetics studies, and the exome sequencing has already been performed. In work package 4, risk of recruitment failure is low as 100 patients will be selected from a database with almost 6,000 patients based on their response to AEDs. The database currently contains 821 patients on CBZ, 587 on VPA, 880 on LEV, and 44 on LCM indicating that the aim of 25 patients per drug can be well achieved. Even if some patients cannot be reached, it will be possible to select alternative patients from the database.

There is a very low risk for obtaining ethics approval. Ethics approvals for pharmacogenetic studies are already in place at all sites. *Partner 1, 2 and 5* also have IRB approval for analysing raw EEG and MRI data. Only *Partners 4 and 6* will need to obtain IRB approval for analysing raw EEG and MRI data. There is a moderate risk that *Partners 4 and 6* will need to re-consent patients for use of raw EEG and MRI data. If that should be the case, patients with most informative data on AED outcome will be prioritised to ensure that all data modalities are available for the most informative patients. However, even if re-consenting is required we expect that inclusion of raw EEG and MRI data will be possible for 50% of the patients which should allow a meaningful assessment of the effect of adding raw EEG and MRI data to the decision support tool.

LIST OF ABBREVIATIONS

AED	antiepileptic drug
ANOVA	analysis of variance
ASD	autism spectrum disorder
AUROC	receiver operator characteristic curve
BAM	binary alignment map

CBZ	carbamazepine
CRF	case report file
CEO	chief executive officer
CSV	comma-separated values
DICOM	digital imaging and communications in medicine
DNA	deoxyribonucleic acid
EC	European Commission
EDF	European data format
EEG	electroencephalogram
EU	European Union
FAIR	findable – accessible – interoperable - reusable
FTE	full time equivalent
GABA	gamma-aminobutyric acid
GATK	genome analysis toolkit
GO	gene ontology
HLA	Human Leukocyte Antigen
ICT	information and communications technology
IMI	innovative medicines initiative
IRB	institutional review board
iPSC	induced pluripotent stem cell
IT	information technology
KEGG	Kyoto encyclopaedia of genes and genomes
LCM	lacosamide
LEV	levetiracetam
MACE	massive analysis of cDNA ends
MGE	medial ganglionic eminence
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
mTOR	mechanistic target of ramamycin
NHGRI	United States National Human Genome Research Institute
PAM	partition around methods
RCT	randomised controlled trial
PI	principal investigator
RNA	ribonucleic acid
RVIS	residual variation intolerance score
SME	small and medium-sized enterprise
UTR	untranslated region
VCF	variant call format
VPA	valproate
WGCNA	weighted gene co-expression network analysis

3.5. DIAGRAM WHICH COMPILES THE WORK PLAN, TIMELINE, SEQUENCING OF WORK PACKAGES, THE CONTRIBUTION OF THE PARTNERS TO EACH WORK PACKAGE AND THEIR INTERACTIONS (TIMEPLAN, GANTT AND/OR PERT, MAX. 1 PAGE)

Timeline RAISE-GENIC			Year 1 months				Year 2 months				Year 3 months			
	Phase	Partner	3	6	9	12	3	6	9	12	3	6	9	12
AIM1	iPSC AED exposure	BEL-P6												
	RNA sequencing	GER-P3												
	Network analysis	GER-P3												
AIM2	Ethics approval for raw EEG and MRI data*	GER-P4												
		BEL-P6												
	AED outcome phenotyping	GER-P4												
		FIN-P5												
		BEL-P6												
	Cluster analysis	GER-P3												
	AIM3	Data homogenisation	CAN-P1											
CAN-P2														
BEL-P6														
Big data analysis		CAN-P2												
Decision support tool development		CAN-P2												
		GER-P3												
Development of web-based app		CAN-P2												
Generation of data repository		CAN-P2												
AIM4	Patient selection and recruitment	CAN-P1												
	Exome sequencing	CAN-P1												
	Decision-support tool evaluation	CAN-P1												
		CAN-P2												
	Multicenter RCT preparation	CAN-P1												
		GER-P4												
		FIN-P5												
		BEL-P6												
	Months		3	6	9	12	15	18	21	24	27	30	33	36

*IRB approval for pharmacogenetic studies is in place at all sites. IRB approval for analysing raw EEG and MRI data is in place at CAN-P1/2 and FIN-P5.

3.6. JUSTIFICATION OF REQUESTED BUDGET AND TOTAL PROJECT COSTS (MAX. 1 PAGE)

General remarks: This proposal relies heavily on already available exome sequencing data of 1382 epilepsy patients provided by *Partners 4-6*. The exploitation of this existing data for re-research on personalised medicine in epilepsy makes it possible to accomplish this large-scale study within the available budget. The proposal also benefits considerably from the existing database at *Partner 1 and 2's* institution allowing the targeted recruitment and genotyping of selected epilepsy patients, who are highly informative regarding treatment outcome, for the confirmation cohort. The availability of these valuable resources is a backbone for success of this highly innovative project.

Partner 1 requires personnel for the recruitment of the most informative patients selected from the database for the confirmation cohort. A clinical research coordinator (1 FTE) will be required for 2 years to contact the patients, arrange written informed consent and obtain the blood samples. A part-time laboratory research assistant (0.25 FTE) for 2 years is mandatory for DNA extraction, biobanking, quality control and preparation of the samples for exome sequencing. In addition, consumables such as DNA extraction kits, solutions, tubes, pipette tips etc. and funding for exome sequencing of the selected 100 samples will be needed. Travel and publication support will be required as well.

Partner 2 requires personnel to perform the big data analysis. A masters level graduate student will be needed for 2 years. Additional funding will be required for subcontracting an SME (Desid Labs Inc., CEO Jordan Engbers) which will provide high-level expertise in data science and advanced analytics. Partner 2 will require further funding for providing the data storage and maintenance through the Clinical Research Unit and Research Computing Services at the University of Calgary. Funding for travel is also needed. Costs for open-access publications will be covered from other sources.

Partner 3 will need a bioinformatic post doc for 2 years to perform the network analysis. The Institution will cover 20% of the position from local funding. Similarly, hardware for computational analysis will be provided by local funds. Additional funding will be required to perform RNA sequencing for 40 samples. Funding for travel and publications are also necessary and will be partially provided by the institute.

Partner 4 will review the medical records of patients with already available exome data from the Epi25 project. To properly categorise treatment response a physician with experience in epilepsy treatment (20 months) will be required for this task. The Institution will cover 20% of the position from local funding. Additional funding will be needed for trial design preparation (year 3), for travel and publications.

Partner 5 requires a post doc researcher for 2 years to provide the outcome data for the patients with available exome sequencing data. In addition, funding for repeat exome sequencing of 10 samples, miscellaneous IT equipment for databasing, travel and publications is requested.

Partner 6 requires a part-time laboratory post doc (0.5 FTE) for 2 years to perform the iPSC cultures, antiepileptic drug exposure experiments and RNA extraction. In addition, cell culture supplies such as flasks, media, growth factors and morphogens, antibodies, immunofluorescence reagents and molecular biology reagents for cell characterization are needed for the iPSC cultures. Furthermore, funding for travel and publications is requested.

3.7. ADDED VALUE OF THE PROPOSED INTERNATIONAL COLLABORATION (MAX. 1 PAGE)

The added value of the consortium is the combination of experts providing a research structure covering all aspects needed to address a personalised medicine approach for AED treatment in epilepsy. The consortium shares expertise in clinical, cellular, genetic, bioinformatic and ICT research and will thus be able to set up an analytical pipeline to identify and treat patients based on a biologically informed decision algorithm for treatment response. The 2-level approach, i.e. the development of novel markers as well as the integration of existing markers, will increase the probability to result in a clinically meaningful decision support tool.

The feasibility of work package (WP) 1 is based on the experience of *Partner 6* in generation and characterization of iPSC as demonstrated in several publications^{23–25,28}. *Partner 3* is an early career scientist and expert in transcriptomic characterization and network identification^{37,38} including drug response³⁹. Previous publications on transcriptomic changes induced by AEDs^{17–21} combined with the experience of *Partner 3* and *6* promise a successful outcome. WP 2 is based on already available exome sequencing data of 1382 individuals with epilepsy provided by *Partners 4, 5* and *6* (tab. 1). *Partners 1* and *4* are clinical epileptologists with extensive experience in phenotyping of patients with genetic epilepsies including treatment response^{40,41} and personalised medicine in epilepsy³. *Partner 1* has been working at the Goethe-University Frankfurt where he has closely collaborated with *Partner 4*, head of the Epilepsy Center Frankfurt. Dr. Philipp Reif, an early career researcher, will take over the lead of the epilepsy genetics working group after *Partner 1*'s move to the University of Calgary in September 2018 and is involved in the project at *Partner 4*'s institution. The existing strong collaboration with *Partner 3* together with the involvement of *Partners 1* and *4* in multiple international consortia including Epicure, EuroEPINOMICS, EpimiRNA, EpiXchange and Epi25 facilitated setting up this unique and highly promising collaborative effort of clinical and basic scientists. *Partners 1, 3* and *4* are part of the Center for Personalized Translational Epilepsy Research funded through the Hessian Ministry of Science and Art^{42,43}. Dr. Chantal Depondt (Professor in the epilepsy unit at *Partner 6*'s institution) is an expert in the characterization of treatment response to AEDs and the harmonization of the outcome data across different centres^{7,15,44–46} which will be paramount for this project. She was responsible for the assessment of AED outcome and adverse drug reactions within the EpiPGX consortium (www.epipgx.eu). Her as well as *Partner 1* and *4*'s experience in clinical phenotyping combined with the knowledge of *Partners 2* and *3* in machine learning techniques, clustering algorithms, and standard genetic risk-score approaches based on available exome sequencing data underpins the feasibility of WP 2. *Partner 2* is an international expert in big data analysis integrating raw diagnostic data such as EEG and MRI. His experience is fundamental for WP 3. He has extensive experience studying large repositories of routinely collected electronic health records data and is exploring the applications of machine learning to better understand the epidemiology of epilepsy^{47–51}. Along with the SME partner Jordan Engbers (CEO of Desid Labs Inc.) who is an expert in data science and advanced analytics, he is creating a personalised medicine and advanced analytics pipeline for epilepsy at the University of Calgary. *Partner 2* will also provide the infrastructure for combining the different data modalities of all partners with strong bio-informatics support through the Clinical Research Unit. The already existing database of the Comprehensive Epilepsy Program in Calgary including drug dosage and seizure frequency at all clinical visits for almost 6000 patients will allow the identification and targeted recruitment of patients for WP 4. *Partner 5* is a clinical epileptologist with an outstanding track record in clinical epilepsy research and a strong background in biomarker research, for which she holds a high-volume grant by the Saastamoinen Foundation. Her expertise and the available IRB to provide raw EEG and MRI biomarker data will be instrumental for the success of this project. The strong local support by Kuopio University Hospital and University of Eastern Finland together with *Partner 4* and *5*'s extensive experience in planning and conduction of clinical trials together with partners from the industry will be helpful to set up the prospective multicentre randomised controlled trial in cooperation with an industry partner^{13,52–54}. Kuopio University Hospital belongs to the European Reference Network for Rare and Complex Epilepsies EpiCARE.

3.8. POTENTIAL IMPACT AND EXPLOITATION OF EXPECTED PROJECT RESULTS (MAX. 1 PAGE)

Epilepsy affects more than 70 million people worldwide of all age groups¹ and is one of the most frequent chronic neurological disorders. Recurrent seizures are a major cause of reduced quality of life due to injuries, death, social stigma as well as vocational and driving restrictions. Antiepileptic drugs are the primary therapy for epilepsy. They operate by reducing the likelihood of seizure occurrence, but their effects show considerable interindividual variation. As the effect of an antiepileptic drug can currently not be predicted in an individual patient, selection of an antiepileptic drug is presently based on trial and error. This results in a reduced chance of seizure freedom. Currently, less than 50% of patients become seizure free with their first antiepileptic drug²².

Our strategy to combine clinical, cellular, genetic, bioinformatic and ICT research for a big data analysis to develop a decision-support tool will revolutionise epilepsy treatment. Physicians will be able to inform their patients about the likelihood to become seizure free with the different drugs. Consequently, patients can make an informed decision which antiepileptic drug they would like to start. Avoiding the trial and error approach, the time until seizure freedom is reached will be considerably shortened resulting in increased quality of life of the patients and decreased costs for health care providers and society.

We expect a strong industry interest in our decision-support tool if intellectual property rights are appropriately protected. We will, therefore, prioritise patenting of the developed approaches. Industry support will be paramount for establishing the decision-support tool in clinical practice to perform a randomised controlled follow-up study and provide the required infrastructure for rapid genetic analysis once epilepsy has been diagnosed.

In this proposal, we focus on predicting the efficacy of four common antiepileptic drugs to show the feasibility of our approach. Once proven successful, our model can be expanded to include other antiepileptic drugs and also side-effects. Furthermore, our strategy can be applied to other diseases facing similar issues as epilepsy. One example are psychiatric diseases where a large number of antipsychotic and antidepressant drugs exist although, similarly to epilepsy, their effect in the individual patient cannot be predicted. Hence, there is a strong prospect of broad applicability of our concept in health care. The clear outcome measure (number of epileptic seizures) sets epilepsy apart from other neuropsychiatric diseases. Therefore, epilepsy will serve as a model disease for implementing personalised medicine and provide the required evidence for future studies in other diseases.

Our preclinical research will not only inform the big data analysis but also provide valuable information on the gene networks implicated in antiepileptic drug response. This knowledge can be incorporated into future drug development and may lead to the development of more efficacious antiepileptic drugs ultimately resulting in improved patient care and quality of life.

3.9. HANDLING OF INTELLECTUAL PROPERTY RIGHTS (E.G. ANY BARRIERS TO SHARING MATERIALS OR RESULTS), BOTH WITHIN AND OUTSIDE THE RESEARCH CONSORTIUM (MAX. ½ PAGE)

The consortium is well aware that publication of research results with open access in the scientific literature is the motor of scientific advance. However, publication of results without patenting the algorithm beforehand will diminish the commercial interest in the algorithms. Implementation of the developed algorithms in clinical practice will require a randomised controlled study, which is only feasible with industry support. To increase the chances of exploitability, which will ultimately lead to successful implementation of the decision support tool in clinical practice, the consortium will, therefore, prioritise patenting of the developed approaches. The partners within the consortium believe that this strategy will be in the best interest of the patients and improve epilepsy therapy in the future. After successful patenting, the results will be published with open access in the scientific literature and disseminated via press and social media. Whenever possible, algorithms will be made available for free non-commercial use.

There are no barriers to share materials or results within the consortium.

3.10. DESCRIPTION OF ON-GOING PROJECTS, PENDING PATENTS AND PATENTS WHEN APPLICABLE OF EACH PARTICIPATING GROUP RELATED TO THE PRESENT TOPIC INDICATING FUNDING SOURCES AND POSSIBLE OVERLAPS WITH PROPOSAL (MAX. 1 PAGE PER GROUP)

Partner 1

Partner 1 will be establishing research projects into personalised medicine in rare monogenic epilepsies at the University of Calgary. These will be funded by start-up support from the University of Calgary and other grant applications. There will be no overlap with RAISE-GENIC as it is addressing common epilepsies. *Partner 1* will also continue to be involved in the Center for Personalized Translational Epilepsy Research funded through the Hessian Ministry of Science and Art (subproject 6, 600 000 € together with *Partner 3*)^{42,43}. As the genetic subproject is focusing on rare monogenic epilepsies there is no overlap with this proposal. *Partner 1* is involved in multiple international and European epilepsy genetics consortia including Epicure, EuroEPINOMICS, EpimiRNA and Epi25 not overlapping with this proposal. He holds no patents and there are no pending patents.

Partner 2

Partner 2 is co-PI on a number of national Canadian initiatives. His major research theme has been the application of 'Big Data', electronic medical records (EMRs), and machine learning as means of advancing the epidemiology of epilepsy and developing outcome-based prediction models. He has received C\$135,000.00 in start-up to use large United Kingdom based EMRs to evaluate the relationship between depression and epilepsy, the association between antiepileptic drugs and psychiatric symptoms, and has developed a clinical decision rule that guides the prescription of levetiracetam in general clinics. He currently has C\$15,000.00 in seed funding from the University of Calgary to create an epilepsy-specific precision medicine pipeline that involves linkage of EEG, MRI, and clinical data. In addition, he has received C\$55,000.00 in funding from the Canadian Frailty Network for exploratory analyses with a few to a future randomised controlled trial of AED use in the elderly with epilepsy. He is head of the Calgary Comprehensive Epilepsy Program registry that contains over 6,000 patients and has secured C\$102,000.00 of funding both to link these data to provincial administrative health records, EEG, and MRI data as well as to create a Canadian consortium whereby standardised data are collected and stored to facilitate multicentre collaboration on observational studies and randomised controlled trials. This research program fits seamlessly with RAISE-GENIC. Using similar methodology, the goal here is to amalgamate and fuse clinical, administrative health, EEG, and MRI data for outcomes prediction including response to a first or second chosen AEDs, emergence of comorbidities, and epi-

lepsy surgical success. Inclusion of a rich variety of biometric data, including raw MRI, EEG, and now genetic data will help enhance the predictive power, impact, and generalizability of all projects falling under this rubric including RAISE-GENIC. Partner 2 holds no patents and there are no pending patents.

Partner 3

Partner 3 is co-PI of the genetics work package in the Center for Personalized Translational Epilepsy Research funded through the Hessian Ministry of Science and Art (subproject 6, 600 000 € together with *Partner 1*)^{42,43}. No cross-funding with this project is available or possible, since *Partner 3* focusses on the functional characterization of genetic variants in-vitro. *Partner 3* is further involved in the child psychiatric consortia for Autism EU-AIMS TRIALS (<https://www.aims-2-trials.eu/> EU funded IMI call) and Self-Injury STAR-NEURO (<https://star-projekt.de/>, funded by the federal ministry of education and research). Within these projects we perform network-based analysis of genetic variants elucidating the underlying biological aetiology as well as to predict treatment response in Autism Spectrum Disorders and Non-Suicidal Self-Injury.

Partner 4

Partner 4 is currently Co-Coordinator of the EpiRNA consortium (<https://www.epimirna.eu>, funded within the FP7 by the EC from 2013-18) investigating the epigenetic role of microRNA in the pathophysiology, treatment and prevention of epilepsy. One patent on the use of mir134 in epilepsy was granted and a second is pending within this consortium. Furthermore, F. Rosenow is the speaker of the Center of Personalized Translational Epilepsy Research funded by the Hessian Ministry of Science and Art from 2018-21 as basis for a Collaborative Research Center proposal. Within this project we aim I) to identify causative genetic variances and acquired aetiologies of individual epilepsies, II) to model these and evaluate precision medicine approaches in animal models and II) if promising, to bring these back to the patients. A strategy for protection and exploitation of acquired intellectual property is in place but relevant results are expected only later during this project. While this project documents our longstanding interest in personalised medicine approaches in epilepsy and will improve our expertise in structured phenotyping, there is no direct overlap of this or the other consortia mentioned with RAISE-GENIC. The engagement in Epi25 mentioned already assures the availability of genotyping data for this project and extends our expertise with repositories such as dbGAP used within Epi25. F. Rosenow is part of the organising committee of the EpiXchange Initiative (<https://www.EpiXchange2018.eu>) which is focused on the promotion of knowledge-finding in epilepsy research by data sharing and other forms of interaction between existing epilepsy/neuroscience consortia. Ideally the repository planned for RAISE-GENIC will be part of the international “epilepsy data ecosystem” to be implemented within this initiative. Partner 4 owns one trademark related to cognitive phenotyping.

Partner 5

Partner 5 collaborates with several national and international research groups including the ILAE Genetics Consortium (<https://www.ilae.org/guidelines/complex-epilepsies>), ENIGMA-Epilepsy (<http://enigma.ini.usc.edu/ongoing/enigma-epilepsy>), a network of imaging genomics, and the Brainstorm Consortium performing the largest ever GWAS-study drawn from more than 200,000 patients for 25 brain associated disorders and 17 phenotypes. In the Human Epilepsy Project (HEP, <http://humanepilepsyproject.org>), which performs multimodal prospective evaluation of biomarkers in newly treated patients with focal epilepsy, Kuopio is one of the few centers from Europe in the HEP1-study and the only center from Europe in the HEP2 study. *Partner 5* is also participating in the Biomarkers of SUDEP project. She collects clinical data and neurophysiological data of patients who experienced sudden unexpected death in epilepsy (SUDEP) and of those at risk of SUDEP within the project "Advancing SUDEP risk prediction using a case-control approach", a worldwide collaboration led by New York University School of Medicine. Together with Aristotle University of Thessaloniki, *Partner 5* develops new protocols and continues to study various generalized and focal epilepsy syndromes and TMS-EEG as epilepsy biomarker. These projects do not overlap with RAISE-GENIC. The collection of the local phenotype-genotype data

and biomarkers in the ongoing “biomarkers of epilepsy” project is funded by grants from the Saastamoinen foundation and from state research funding (total 1,500,000 €). Her engagement in Epi25 assures the availability of genotyping data for this project.

Partner 6

Partner 6 is currently developing and validating protocols to generate different neuronal types, including cortical, cerebellar, and primary sensory neurons from iPSCs. This work is a component of translational research projects on Friedreich ataxia, currently supported by the FNRS and the charity FARA, for cerebellar and sensory neurons. There is no overlap with RAISE-GENIC addressing cortical, in particular glutamatergic and GABAergic, neurons.

Partner 6 is also actively involved as a PI and collaborator in the following international research consortia on epilepsy genetics and pharmacogenetics: EpiPGX, Epigen, CENet, Epi25, ENIGMA, and the Consortium on Genetics of Complex Epilepsies of the International League Against Epilepsy (ILAE). None of these projects considers response to individual AEDs from a network perspective; therefore there is no overlap with the current proposal.

3.11. PATIENT INVOLVEMENT (MAX. ½ PAGE)

The consortium will maximise patient involvement by inviting one patient representative from each participating country (Belgium, Canada, Finland, Germany) as advisory board members. These will provide valuable advice on patient-oriented aspects of the research that will be particularly important when transferring the research results into clinical practice. However, the consortium will also benefit from advice during the early phase of the proposal as incorporating patient-oriented aspects at this stage will ensure that the results can be smoothly transitioned to routine clinical care.

In addition, stakeholders and patient representatives will be invited to yearly project meetings and their suggestions incorporated into the research program whenever possible. Patient awareness and science education will be promoted by publishing lay summaries of research results on the internet and via social media.

3.12. INCLUSION OF GENDER AND/OR SEX ANALYSIS (MAX. ½ PAGE)

The development of decision support tools for epilepsy treatment will be of benefit for both sexes. Sex appears to have a profound role on the expression of seizures. While gender plays a limited role in the pathophysiology of epilepsy it will be an important characteristic to examine (i.e. through patient reported outcomes) when launching the decision support tools into routine care. Specific factors will be considered by performing the preclinical studies in female and male iPSCs separately and by including sex as a covariate when performing the big data analysis. Ultimately, the decision support tools will incorporate sex as well as gender aspects when providing individualised treatment recommendations.

The consortium intentionally made the decision to include VPA in the proposal although it is known that VPA has teratogenic effects and is, therefore, problematic in females of childbearing age. On the other hand, VPA is still widely used as it is considered to be the first choice in generalised epilepsy. However, the effect in the individual patient cannot be predicted and it is often possible to use different drugs such as LEV. It would greatly improve treatment in females of childbearing age if it was possible to predict the likelihood of success of the different antiepileptic drugs including VPA. If the likelihood of seizure freedom was considerably higher for VPA than other antiepileptic drugs, females, who are not planning a pregnancy in the near future, may choose VPA as their first antiepileptic drug and change to a different drug later on before becoming pregnant. On the other hand, if other antiepileptic drugs are predicted to have a higher or similar likelihood of success, VPA can be avoided without concern. Therefore, the ability to predict the efficacy of VPA will provide valuable information to female epilepsy patients for making an informed decision about their epilepsy treatment during childbearing age.

The consortium will strive for even gender distribution of research personnel and the advisory board. The availability of part-time positions will ensure the compatibility of family and research.

3.13. ETHICAL ISSUES OF THE PROJECT PROPOSAL (MAX. ½ PAGE)

The 1382 patients, who were included and exome sequenced within the Epi25 collaborative, had provided written informed consent prior to inclusion in Epi25. The study was approved by all relevant institutional reviews boards. As the consent also included pharmacogenetics research all 1382 patients can be included in this proposal without further consent. Transfer of the phenotypic data on the epilepsy and outcome on antiepileptic drugs for analysis is included in the consent as well. 977 of the 995 patients of Partner 4 and 5 have also consented to be re-contacted. The remaining 387 patients of Partner 6 do not need to be re-phenotyped as AED outcome data is already available. As it was a requirement for inclusion in Epi25 that patients recruited after January 25, 2015 had consented to deposition of the data in databases with restricted access to facilitate follow-up studies, consent to deposit the data in a repository, as planned in this proposal, is available for these samples and the data has already been deposited or is in the process of being deposited into the dbGAP database by the Epi25 collaborative. Patients recruited before January 25, 2015 were re-contacted within Epi25 and asked for permission to database deposition. In total, consent to deposit the data in a data repository is available for 1240 samples. IRB approval for pharmacogenetics studies is also in place at *Partner 1 and 2's* institution.

The status of the ethics approval for incorporating raw EEG and MRI into the analysis varies between the Partners. At *Partner 1, 2 and 5's* institution approval for analysing raw EEG and MRI has already been granted and is included in the consent. *Partners 4 and 6* will apply for ethics approval for providing raw EEG and MRI data. If re-consenting of the patients is required by the institutional review board, *Partners 4 and 6* will re-contact selected most informative patients and obtain written informed consent.

The European Commission (EC) has recognised Canada as providing an adequate level of data protection permitting transfer of personal (i.e. genetic) data to Partner 1 and 2. Should any changes in Canada's status occur as a result of the current General Data Protection Regulation, the partners will establish contractual clauses safeguarding data protection following current EC recommendations.

3.14. DATA MANAGEMENT STRATEGY/PLAN¹ (MAX. 2 PAGE)

Description of the data: The proposed study will combine preclinical research studies, biomarker studies and cohort studies and, therefore, generate multiple types of data:

Work package 1: Quantitative gene expression data from AED treated and control iPSCs, qualitative and quantitative data resulting from the network analysis of the expression data

Work package 2: Qualitative and quantitative outcome data on AED treatment categorised using the EpiPGX CRF, qualitative and quantitative phenotypic data on the epilepsy as obtained on the Epi25 CRF, quantitative and qualitative data on biomarkers, raw EEG and MRI data, qualitative and quantitative data resulting from the cluster analysis, qualitative exome sequencing data

Work package 3: Algorithms used for the decision support tool

Work package 4: Qualitative and quantitative outcome data on AED treatment categorised using the EpiPGX CRF, qualitative and quantitative phenotypic data on the epilepsy as obtained on the Epi25 CRF, quantitative and qualitative data on biomarkers, raw EEG and MRI data, qualitative exome sequencing data, qualitative data on the performance of the decision support tools

The following standard formats will be used: FASTQ files raw reads mRNA sequencing; raw count matrix format (CSV): gene expression data, VCF file: exome data, EpiPGX CRF format (RedCap): AED outcome data, Epi25 CRF format (RedCap): epilepsy phenotypic data, DICOM file: raw MRI data, EDF file: raw EEG data, other formats depending on the results of the different analyses, whenever possible non-proprietary formats such as the CSV table format will be used to facilitate data sharing.

Data collection/generation/reuse: The project will reuse exome data generated within the Epi25 project. The data (VCF and BAM files) have already been provided to *Partners 4-6* and can be readily provided to *Partner 2* and *3* for analysis. The project will also reuse data on AED outcome already obtained by *Partner 6* in the EpiPGX CRF format. Also, it will make use of the existing database at *Partner 1 and 2's* institution. The database will be queried with support of the Clinical Research Unit at *Partner 1 and 2's* institution to identify the most informative patients for recruitment in Work package 4.

Gene expression data from iPSC cells treated with AEDs is paramount for identification of the gene networks involved in AED response. It will be obtained from 2 cell lines for each AED and with 2 technical replicates each to minimise error. The data will be generated and analysed by *Partner 3*. The data and results thereof will also be provided as CSV files to *Partner 2* for the big data analysis. Since FASTQ files from RNA sequencing analysis do contain sequence information and allow a re-identification of individuals, these files will not be shared outside the consortium. The AED outcome data is a prerequisite for developing personalised medicine approaches in epilepsy. This data will be obtained from clinical records by *Partners 1, 4 and 5*. Experienced personnel will review the clinical records and categorise treatment response and adverse effects using the well-established EpiPGX CRF which will be hosted at *Partner 1 and 2's* institution. The entered data will be reviewed by *Partner 1, 2 and 6* to ensure validity and comprehensiveness.

The raw EEG and MRI data required for the big data analysis will be obtained at *Partner 1, 4, 5 and 6* and transferred to *Partner 2*. EEG will be converted into the EDF (European Data Format). MRI data will be in DICOM format.

Exome sequencing data in the replication cohort is necessary to apply and test the decision support tool in this cohort. The data will be provided using the VCF and BAM format.

Data management, documentation and curation: The Clinical Research Unit and Research Computing Services at *Partner 1 and 2's* institution will be responsible for central storage and management of all data used and generated within this project. Data will be kept in 2 copies in 2 locations with 15 min asynchronous replication and additional hourly backups. The following main types of data will be stored: 1. Exome sequencing data (VCF format), 2. Gene expression data

¹ For more information please consult:

http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf

(FASTQ and raw count matrix as CSV file), 3. Phenotypic data (EpiPGX CRF, Epi25 CRF, stored in RedCap database), 4. Raw EEG and MRI data (EDF and DICOM format), 5. Analysis results in varying formats (CSV files if possible). The stored data will be accompanied by metadata describing the type of data, how it was generated and the content of each data field. Data arising from the same individual will be pseudo-anonymised and labelled with the same identifier to allow combined analysis.

The data storage will be maintained for the duration of the project. Subsequently, the data will be transferred into a repository with restricted access. Personal data that may allow re-identification of a patient (genetic, MRI) will only be transferred if written informed consent for database storage is available. The consortium plans to take advantage of the data sharing facilities that will be implemented by the EpiXchange initiative. This is expected to be free of charge for EU-funded consortia. However, should funding be required the consortium will provide the cost for 5 years from own funds. The costs will be shared between all partners.

Data security and confidentiality of potentially disclosive information: Data will be encrypted during transit (SMB 3.0 or NFS 4 with Kerberos 5p) and at rest (unique encryption key for each project). Access to the different types of data will be granted only to the users requiring access for conduction of their research projects. User access control will be managed through AD security groups. The hardware is stored in secured datacentres, with access controls and physical locks on each rack.

The major risk would be the re-identification of probands participating in the research project based on genetic or MRI data. Such a re-identification would only be possible if the attacker has additional genetic or imaging information on the participants that is linked to other identifying data. This would for example be the case if the probands had uploaded genetic data linked to their personal information on the internet for example for genealogic research. To avoid this risk, we will ensure that only individuals involved in the proposal, who have obligated to refrain from trying to re-identify probands, will have access to the data. Proband data is only transferred to a restricted-access repository if the probands have provided written consent after being informed about this risk. Consent for data deposition is already available for 1240 samples. All data is pseudonymised and the key linking personal data to research data will be stored at the recruiting site on an independent virtual area network, not accessible through the standard data repository network and not shared within the consortium.

Data sharing and access: After completion of the research work outlined in the proposal, the consortium will setup a data repository to ensure sustainability and facilitate follow-up studies (*REUSABLE*). These may address additional AEDs not investigated in this proposal or pharmacogenetic studies on side effects. We plan to take advantage of the “epilepsy data ecosystem” including data sharing facilities that will be implemented by the EpiXchange initiative before the end of this proposal. The data repository will contain data of the gene expression analysis and results of the network, cluster and big data analysis. If patients have provided written informed consent for data storage in restricted-access data repositories (already available for 1240 samples), their exome sequencing, phenotypic, biomarker, raw EEG and raw MRI data will be deposited in the repository as well using the outlined data formats (*INTEROPERABLE*).

As outlined in 3.9, the consortium will prioritise patenting of the developed approaches to increase the chances of exploitability. We estimate that intellectual property rights will have been secured 2 years after the end of the project. Subsequently, access to the repository for other researchers will be granted upon request to the steering committee. The steering committee will consist of all partners of the proposal and decide by majority vote. Access to the repository will only be granted if the proposed study is sound and the investigators guarantee data security and confidentiality as set out in data sharing agreements (*ACCESSIBLE*).

A summary of the included data will be published on the webpages of the project and the EpiXchange initiative to ensure that interested researchers are able to find the repository (*FIND-ABLE*) assuring all aspects of the FAIR principle.

Responsibilities: All issues regarding study-wide data management, metadata creation, data security and quality assurance of data will be governed by the RAISE-GENIC steering committee.

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5. FINANCIAL PLAN OF PROJECT BUDGET (IN €¹): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Please note that **not** all types of expenditure are fundable by all funding organisations (see the “Guidelines for applicants” for details on the eligibility criteria and/or contact the relevant ERA PerMed national/regional funding organisation). Thousand separators and whole numbers should be used only (e.g. 200.000).

Partners	Coordinator Partner 1		Partner 2		Partner 3		Partner 4		Partner 5		Partner 6		Part-ner 7			
Name (group leader)	Karl Martin Klein		Colin Josephson		Andreas Chiocchetti		Felix Rosenow		Reetta Kälviäinen		Massimo Pandolfo		-			
Institution	University of Calgary		University of Calgary		Goethe University Frankfurt		Goethe Universi-ty Frankfurt		University of Eastern Finland		Université Libre de Bruxelles					
Country	Canada		Canada		Germany		Germany		Finland		Belgium					
Funding organisation	Canadian Institutes of Health Research		Canadian Institutes of Health Research		Federal Ministry of Education and Re-search (BMBF)		Federal Ministry of Education and Research (BMBF)		Academy of Fin-land (AKA)		Fund for Scientific Research (F.R.S.-FNRS)					
PROJECT COSTS (€)	Total cost	Requested	Total cost	Requested	Total cost	Requested	Total cost	Requested	Total cost	Request-ed	Total cost	Requested			Total	Requested
Personnel €	125,000 (\$187,933)	125,000 (\$187,933)	26,500 (\$40,000)	26,500 (\$40,000)	139,800	111,840	154,080	123,264	148,564	103,995	90,000	90,000			683,944	580,599
Consumables €	2,000 (\$3,000)	2,000 (\$3,000)	0	0	0	0	0	0	790	553	106,000	106,000			108,790	108,553
Equipment €	0	0	0	0	2,000	0	0	0	0	0	0	0			2,000	0
Travel € ²	4,000 (\$6,000)	4,000 (\$6,000)	4,000 (6,000)	4,000 (6,000)	2,000	1,000	2,000	0	6,022	4,215	2,000	2,000			20,022	15,215
Other direct costs € ³	68,000 (\$102,250)	68,000 (\$102,250)	68,750 (\$103,125)	67,250 (\$100,875)	14,352	13,852	1,500	0	10,000	7,000	1,500	1,500			164,102	157,602
Overheads € ⁴	0	0	0	0	31,630	25,388	31,516	24,653	120,337	84,236	0	0			183,483	134,227
Total	199,000 (\$299,183)	199,000 (\$299,183)	99,250 (\$149,125)	97,750 (\$146,875)	189,782	152,030	189,096	147,917	285,713	200,000	199,500	199,500			1,162,341	996,197

1 Those countries whose currency is different than € shall include their national currency in brackets

2 Please take into account that coordinators (and partners) shall present the projects at a midterm or final ERA PerMed symposium

3 E.g. subcontracting, provisions, licensing fees; may not be eligible costs in all countries (will be handled according national regulations)

4 Overhead costs: funding according to national regulations

5.1. FINANCIAL PLAN OF COORDINATOR - PROJECT PARTNER 1 (IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Type	Item Description	Total	
		Total costs	Requested
Personnel <i>Please specify (e.g. PhD students, Post Doc researchers, technicians and the number of Person-Months)</i>	1 FTE clinical research coordinator for 2 yrs: 24 person-months 0.25 FTE laboratory research assistant for 2 yrs: 6 person-months	125,000 (\$187,933)	125,000 (\$187,933)
Consumables <i>Please specify (e.g. reagents, kits, antibodies, cell culture material, animals etc.)</i>	DNA extraction kits, solutions, tubes, pipette tips	2,000 (\$3,000)	2,000 (\$3,000)
Equipment <i>Please specify equipment</i>	Nil	0	0
Travel <i>Please specify (e.g. allowances, meeting fees etc.)</i>	2 international, 2 national meetings (including yearly project meetings)	4,000 (\$6,000)	4,000 (\$6,000)
Other <i>Please specify (e.g. animal costs, subcontracting, provisions, licensing fees, patents, publications, etc.)</i>	Exome sequencing (100 samples à C\$1000) Open access publications 2 à 750 €	68,000 (\$102,250)	68,000 (\$102,250)
Overhead*	Nil	0	0
Total		199,000 (\$299,183)	199,000 (\$299,183)

* Please note that there is not a common flat rate for the overhead category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for applicants" or contact your relevant funding agency for further information.

5.2. FINANCIAL PLAN OF PROJECT PARTNER 2 (IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Type	Item Description	Total	
		Total costs	Requested
Personnel <i>Please specify (e.g. PhD students, Post Doc researchers, technicians and the number of Person-Months)</i>	1 Masters level graduate student: 24 person-months	26,500 (\$40,000)	26,500 (\$40,000)
Consumables <i>Please specify (e.g. reagents, kits, antibodies, cell culture material, animals etc.)</i>	Nil	0	0
Equipment <i>Please specify equipment</i>	Nil	0	0
Travel <i>Please specify (e.g. allowances, meeting fees etc.)</i>	2 international, 2 national meetings (including yearly project meetings)	4,000 (\$6,000)	4,000 (\$6,000)
Other <i>Please specify (e.g. animal costs, subcontracting, provisions, licensing fees, patents, publications, etc.)</i>	- Subcontracting Desid Labs Inc. (C\$150.00/hr * 450 hours) - Storage and maintenance of data in the University of Calgary's Clinical Research Unit and Research Computing Services (C\$10,000/year * 3 years) - Open access publications 2 à 750 € (covered from own funds)	68,750 (\$103,125)	67,250 (\$100,875)
Overhead*	Nil	0	0
Total		99,250 (\$149,125)	97,750 (\$146,875)

* Please note that there is not a common flat rate for the overhead category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for applicants" or contact your relevant funding agency for further information.

5.3. FINANCIAL PLAN OF PROJECT PARTNER 3 (IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Type	Item Description	Total	
		Total costs	Requested
Personnel <i>Please specify (e.g. PhD students, Post Doc researchers, technicians and the number of Person-Months)</i>	1 Bioinformatic post doc (E13 ST 3-4): 24 Person-Months	139,800	111,840
Consumables <i>Please specify (e.g. reagents, kits, antibodies, cell culture material, animals etc.)</i>	Nil	0	0
Equipment <i>Please specify equipment</i>	High performance computer	2,000	0
Travel <i>Please specify (e.g. allowances, meeting fees etc.)</i>	2 international, 2 national meetings (including yearly project meetings)	2,000	1,000
Other <i>Please specify (e.g. animal costs, subcontracting, provisions, licensing fees, patents, publications, etc.)</i>	RNA Seq of 40 Samples: 2 cell lines, 2 cell types 4 AEDs +1 control condition and two technical replicates. Open access publications 2 à 750 €	14,352	13,852
Overhead*		31,630	25,388
Total		189,782	152,030

* Please note that there is not a common flat rate for the overhead category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for applicants" or contact your relevant funding agency for further information.

5.4. FINANCIAL PLAN OF PROJECT PARTNER 4 (IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Type	Item Description	Total	
		Total costs	Requested
Personnel <i>Please specify (e.g. PhD students, Post Doc researchers, technicians and the number of Person-Months)</i>	MD with epilepsy experience for phenotyping (Ä2-Ä3) : 20 Person-Months	154,080	123,264
Consumables <i>Please specify (e.g. reagents, kits, antibodies, cell culture material, animals etc.)</i>	Nil	0	0
Equipment <i>Please specify equipment</i>	Nil	0	0
Travel <i>Please specify (e.g. allowances, meeting fees etc.)</i>	2 international and 2 national meetings (including yearly project meetings)	2,000	0
Other <i>Please specify (e.g. animal costs, subcontracting, provisions, licensing fees, patents, publications, etc.)</i>	Open access publications 2 à 750 €	1,500	0
Overhead*		31,516	24,653
Total		189,096	147,917

* Please note that there is not a common flat rate for the overhead category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for applicants" or contact your relevant funding agency for further information.

5.5. FINANCIAL PLAN OF PROJECT PARTNER 5 (IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Type	Item Description	Total	
		Total costs	Requested
Personnel <i>Please specify (e.g. PhD students, Post Doc researchers, technicians and the number of Person-Months)</i>	1 Post Doc Researcher: 24 Person-Months	148,564	103,995
Consumables <i>Please specify (e.g. reagents, kits, antibodies, cell culture material, animals etc.)</i>	Miscellaneous IT equipment	790	553
Equipment <i>Please specify equipment</i>	Nil	0	0
Travel <i>Please specify (e.g. allowances, meeting fees etc.)</i>	2 international and 2 national meetings (including yearly project meetings)	6,022	4,215
Other <i>Please specify (e.g. animal costs, subcontracting, provisions, licensing fees, patents, publications, etc.)</i>	Open access publications 2 à 750 € Exome sequencing of appr. 10 samples if repeated sequencing is needed	10,000	7,000
Overhead*		120,337	84,236
Total		285,713	200,000

* Please note that there is not a common flat rate for the overhead category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for applicants" or contact your relevant funding agency for further information.

5.6. FINANCIAL PLAN OF PROJECT PARTNER 6 (IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Type	Item Description	Total	
		Total costs	Requested
Personnel <i>Please specify (e.g. PhD students, Post Doc researchers, technicians and the number of Person-Months)</i>	50% laboratory post doc for 2 years: 12 Person-Months	90,000	90,000
Consumables <i>Please specify (e.g. reagents, kits, antibodies, cell culture material, animals etc.)</i>	Cell culture supplies (flasks, media, growth factors and morphogens, antibodies, immunofluorescence reagents, molecular biology reagents for cell characterization)	106,000	106,000
Equipment <i>Please specify equipment</i>	Nil	0	0
Travel <i>Please specify (e.g. allowances, meeting fees etc.)</i>	2 international and 2 national meetings (including yearly project meetings)	2,000	2,000
Other <i>Please specify (e.g. animal costs, subcontracting, provisions, licensing fees, patents, publications, etc.)</i>	Open access publications 2 à 750 €	1,500	1,500
Overhead*	Nil	0	0
Total		199,500	199,500

* Please note that there is not a common flat rate for the overhead category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for applicants" or contact your relevant funding agency for further information.

5.7. FINANCIAL PLAN OF PROJECT PARTNER 7 (IN €): PLEASE MAKE SURE THAT THE SAME FIGURES ARE ENTERED IN THE SECTIONS THAT NEED TO BE COMPLETED ONLINE (PT-OUTLINE SUBMISSION TOOL)

Only in case of inclusion of partners from underrepresented countries. These partners must be eligible research groups from the following funding organisations: Canada (FRQS, CIHR), Croatia (MSE), Estonia (ETAg), Germany (Saxony), Italy (Lombardy, FRRB), Romania (UEFISCDI), Spain (GN), Spain (CDTI), Turkey (TUBITAK).

None

* Please note that there is not a common flat rate for the overhead category given by the ERA PerMed call. It may vary according to each funding agency's regulations; please check the "Guidelines for applicants" or contact your relevant funding agency for further information.

6. BRIEF CVs OF CONSORTIUM PARTNERS

For each of the consortium partners, please provide a brief CV for the Project Consortium Coordinator and each Project Partner Principal Investigator with a list of up to five relevant publications within the last five years demonstrating the competence to carry out the project (max 1 page each, complete form below).

6.1. COORDINATOR – PROJECT PARTNER 1

Last Name	Klein
First Name	Karl Martin
Institution	University of Calgary (from September 2018)
Short CV	<p>Professional and University Career</p> <p>Associate Professor, Department of Clinical Neurosciences, University of Calgary, Canada, from September 2018</p> <p>Consultant, Epilepsy Center Frankfurt Rhine-Main, 2015-2018</p> <p>Habilitation in Neurology, Philipps University Marburg, Germany, 2014</p> <p>Chamber-certification in Neurology, 2014</p> <p>Clinical training in Neurology, Philipps University Marburg, Germany, 2013-2015</p> <p>Clinical training in Psychiatry, Vitos Klinik für Psychiatrie und Psychotherapie, Marburg, Germany, 2012-2013</p> <p>Clinical training in Neurology, Philipps University Marburg, Germany, 2011-2012</p> <p>Doctor of Philosophy (PhD), University of Melbourne, Australia, 2012</p> <p>Research Fellowship, Epilepsy Research Centre, Austin Health, University of Melbourne, Australia, 2008-2011</p> <p>MD (Dr. med.), Philipps University Marburg, Germany, 2003</p> <p>Clinical training in Neurology, Philipps University Marburg, Germany, 2002-2008</p> <p>Medical School, Philipps University Marburg, Germany, 1996-2002</p> <p>Grants</p> <p>Subproject on identification and functional analysis of susceptibility genes for epilepsy, 600 000 € as PI together with Dr. Andreas Chiocchetti, within the Center for Personalized Translational Epilepsy Research (CePTER). Funded through the Hessian Ministry of Research and Art's LOEWE initiative. Total funding 4.7 Mio €, 2018-2021</p> <p>Co-applicant EpimiRNA consortium (www.epimirna.eu): WP 5: miRNA Genetic Variation in Human Epilepsy. Funded through the European Union's Seventh Framework Programme (FP7), EpimiRNA Grant Agreement no. 602130. Total funding: 11.5 Mio €, Philipps-University Marburg 3 Mio €, 2013-2018</p>
List of five relevant publications within the last five years	<p>Total citations 2194, h-index 20 (Google Scholar, July 2018)</p> <p>Full list: http://orcid.org/0000-0002-6654-1665</p> <ol style="list-style-type: none"> 1. Rosenow F, ..., Chiocchetti A, ..., Klein KM, ..., Reif PS et al. Personalized translational epilepsy research - Novel approaches and future perspectives: Part I: Clinical and network analysis approaches. <i>Epilepsy & Behavior</i> 2017;76:13-18. 2. Klein KM, ..., Rosenow F et al. for the Israeli-Palestinian Epilepsy Family Consortium. The phenotypic spectrum of ARHGEF9 includes intellectual disability, focal epilepsy and febrile seizures. <i>Journal of Neurology</i> 2017;264:1421-1425. 3. Reif PS, ..., Rosenow F, Klein KM. Precision medicine in genetic epilepsies: break of dawn? <i>Expert Reviews of Neurotherapeutics</i> 2017;17:381–392. 4. Dibbens LM, ..., Klein KM et al. Mutations in DEPDC5 cause familial focal epilepsy with variable foci. <i>Nature Genetics</i> 2013;45:546-551. 5. Klein KM, Bromhead CJ, Smith KR, O'Callaghan CJ, Corcoran SJ, Heron SE, Iona X, Hodgson BL, McMahon JM, Lawrence KM, Scheffer IE, Dibbens LM, Bahlo M, Berkovic SF. Autosomal dominant vasovagal syncope: Clinical features and linkage to chromosome 15q26. <i>Neurology</i> 2013;80:1485-1493.

6.2. PROJECT PARTNER 2

Last Name	Josephson
First Name	Colin
Institution	University of Calgary
Short CV	<p><u>Professional and University Career</u></p> <p>2016-: University of Calgary, Calgary, AB, Canada (Assistant Professor Neurology)</p> <p>2015: University College London, London, UK (Internship in Health Informatics)</p> <p>2013-15: University of Calgary, Calgary, Alberta, Canada (Epilepsy Fellowship)</p> <p>2009-11: University of Edinburgh, Edinburgh, UK (Vascular Neurology Fellowship)</p> <p>2006-13: Dalhousie University, Halifax, Nova Scotia, Canada (FRCPC Neurology)</p> <p>2002-06: Dalhousie University, Halifax, Nova Scotia, Canada (MD)</p> <p>2000-03: McGill University, Montreal, Quebec, Canada (MSc)</p> <p>1996-2000: Queen's University, Kingston, Ontario, Canada (BSch)</p> <p><u>Honours and Awards</u></p> <p>2017: International League Against Epilepsy (ILAE) Leadership Program</p> <p>2014: Susan S. Spencer Clinical Research Training Fellowship in Epilepsy</p> <p>2010: European Stroke Conference Young Investigator of the Year Award.</p> <p><u>National and International Committees</u></p> <p>2017-: International League Against Epilepsy Task Force on Big Data/Open Data</p> <p>2017-: International League Against Epilepsy Sub-Task Force on Driving with Epilepsy</p> <p><u>Grants</u></p> <p>2018: University of Calgary Research Grants Committee Seed Grant; \$15,000.00</p> <p>2018: University of Calgary Hotchkiss Brain Institute; \$15,000.00 (CAD)</p> <p>2018: UCB Canada Inc. grant for the CANadian Observational study on Epilepsy (CANOE); \$102,000.00 (CAD)</p> <p>2014-17: Alberta Innovates: Health Solutions Clinician Fellowship; \$210,000.00</p> <p>2014-16: Canadian Institutes of Health Research Fellowship; \$165,000.00 (CAD)</p> <p>2014-16: Canadian Society of Clinical Neurophysiologists Clinical Fellowship</p>
List of five relevant publications within the last five years	<p>Total citations: 809; h-index 12 (Google Scholar July 2018)</p> <p>Pubmed: https://www.ncbi.nlm.nih.gov/pubmed/?term=josephson+colin+OR+josephson+cb Google scholar: https://scholar.google.ca/citations?user=8M_5zcYAAAAJ&hl=en</p> <ol style="list-style-type: none"> 1. <u>Josephson CB</u> et al. Serotonin reuptake inhibitor use and mortality in epilepsy: findings from a contemporary linked electronic health records cohort study. <i>Epilepsia</i> 2017; 58(11):2002-2009. 2. <u>Josephson CB</u>, et al. Association of depression and treated depression with epilepsy and seizure outcomes: a multi-cohort analysis. <i>JAMA Neurology</i> 2017; 74(5):533-39. 3. <u>Josephson CB</u> et al. Towards a clinically informed, data driven definition of elderly-onset epilepsy. <i>Epilepsia</i> 2016; 57(2): 298-305. 4. <u>Josephson CB</u>, Engbers J, et al. An investigation into the psychosocial effects of the postictal state. <i>Neurology</i> 2016; 86(8): 723-30. 5. <u>Josephson CB</u>, et al. Systematic review and meta-analysis of standard vs selective temporal lobe epilepsy surgery. <i>Neurology</i> 2013; 80(18): 1669-76.

6.3. PROJECT PARTNER 3

Last Name	Chiocchetti
First Name	Andreas G
Institution	Goethe-University Frankfurt, Germany
Short CV	<p>Professional and University Career Head of the Molecular Genetics Laboratory at the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Frankfurt; since Oct 2011 Visiting research scholar at the University of California Los Angeles, Gonda Institute of Neuroscience, Laboratory of Dr. Daniel Geschwind; winter-term 2014/15 External lecturer for Biology at the federal school for technical assistants at the University Hospital Frankfurt; Oct 2014 to April 2017 PhD Degree (Dr. rer. nat.) in Genetics; working at the German Cancer Research Center, Division of Molecular Genome Analysis, Heidelberg, Germany, awarded by the University of Salzburg, Austria; 2011 Master Degree (MA. rer. nat.) in Genetics and Biotechnology, University of Salzburg, Austria; 2007</p> <p>Grants LOEWE Center for Personalized Translational Epilepsy Research (CePTER): Co-PI Subproject 6 (600 000 €) with KM Klein; Hessian Ministry of Research and Art. Total 4.7 Mio €, Coordinator F Rosenow, 2018-21 Subproject on genotyping and analysis of genetic variants in patients with non-suicidal self-injury (73 593 €); BMBF-funded project STAR (Self-injury: Treatment, Assessment, Recovery; Total volume 3.3 Mio € to P Plener FP7 „FemNat-CD“ project ; “Neurobiology and treatment of Adolescent Female Conduct Disorder”. Sub-Task WP2 Genetic, Epigenetics and Environment; 900 000 € (Total 6 Mio € to CM Freitag). Ended Feb 2018 EU Funded IMI Grant AIMS-2-TRIAL “Personalized treatment strategies in autism spectrum disorders”; 780 000 € to C Ecker, CM Freitag and AG Chiocchetti (total Volume 60 Mio € to D Murphy, UK) <u>Awards:</u> Price for young Scientists in the field of human medicine (Dr. Paul und Cilly Weill-Foundation)</p>
List of five relevant publications within the last five years	<p>Total citations 2270, h-index 17 (Google Scholar, July 2018) Full list: https://scholar.google.de/citations?user=PgpbvXYAAAAJ</p> <ol style="list-style-type: none"> 1. Kranz TM, Kopp M, Waltes R, Sachse M, Duketis E, Jarczok TA, Degenhardt F, Görgen K, Meyer J, Freitag CM, Chiocchetti AG. Meta-analysis and association of two common polymorphisms of the human oxytocin receptor gene in autism spectrum disorder. <i>Autism Res.</i> 2016;9:1036-1045 2. Chiocchetti AG, Haslinger D et al. Transcriptomic signatures of neuronal differentiation and their association with risk genes for autism spectrum and related neuropsychiatric disorders. <i>Transl Psychiatry.</i> 2016;6:e864. 3. Chiocchetti AG, Kopp M, Waltes R, Haslinger D et al. Variants of the CNTNAP2 5' promoter as risk factors for autism spectrum disorders: a genetic and functional approach. <i>Mol Psychiatry.</i> 2015;20:839-49. 4. Waltes R, Gfesser J, Haslinger D, Schneider-Momm K, Biscaldi M, Voran A, Freitag CM, Chiocchetti AG. Common EIF4E variants modulate risk for autism spectrum disorders in the high-functioning range. <i>J Neural Transm (Vienna).</i> 5. Chiocchetti AG, Haslinger D et al. Protein signatures of oxidative stress response in a patient specific cell line model for autism. <i>Mol Autism.</i> 2014 Feb 10;5(1):10. doi: 10.1186/2040-2392-5-10. PubMed PMID: 24512814; PubMed Central PMCID: PMC3931328.

6.4. PROJECT PARTNER 4

Last Name	Rosenow
First Name	Felix
Institution	Goethe-University Frankfurt, Germany
Short CV	<p><u>Professional and University Career</u> Director, Epilepsy Center Frankfurt Rhine-Main and Associate Professor, Goethe-University Frankfurt, Faculty of Medicine, since 2015 Master of Health Business Administration University Erlangen-Nürnberg 2012 Associate Professor, Philipps-University Marburg, Faculty of Medicine, since 2015 Habilitation in Neurology, Philipps University Marburg, Germany, 1998 Head, Epilepsy Center Hessen-Marburg 1997-2015 Clinical Fellowship, Section of Epilepsy and Sleep, Department of Neurology, The Cleveland Clinic Foundation, Cleveland, USA, 1995-1997 Chamber-certification in Neurology, 1994 Clinical training in Neurology and Psychiatry (1 year), University of Cologne, Germany, 1988-89 and 1990-1994 MD (Dr. med.), University of Cologne, Germany, 1992 MD-theses research stipend of the Max-Planck-Institute for Neurological Research, Cologne, Germany 1989 Medical School, Free University of Berlin, Germany, 1982-1988</p> <p><u>National and International Committees</u> 2018- 2nd Vice-President DGKN (German Society for Clinical Neurophysiology) 2018- ILAE, Task Force on evidence based epilepsy surgery</p> <p><u>Grants</u> Coordinator, EpilepsieNetz Hessen (Telemedicine network project), funded through the Hessian Ministries of Social Affairs and Integration and of Research and Art. Total funding 750,000 €; 2018 – 2021 Coordinator, Center for Personalized Translational Epilepsy Research (CePTER), funded through the Hessian Ministry of Research and Art's LOEWE initiative. Total funding 4.7 Mio €; 2018 – 2021 Co-Coordinator, EpimiRNA consortium (www.epimirna.eu): Funded through the European Union's Seventh Framework Programme (FP7), Grant Agreement no. 602130. Total funding: 11.5 Mio €, Philipps-University Marburg 3 Mio €, 2013 – 18</p>
List of five relevant publications within the last five years	<p>535 Publications, 10497 citations, H-index 49 (Google Scholar, February 2018) Full list: https://www.ncbi.nlm.nih.gov/pubmed/?term=Rosenow+F Blumcke I, ..., Rosenow F et al. Histopathological Findings in Brain Tissue Obtained from Epilepsy Surgery. <i>New Engl J Med</i>, 2017 377(17):1648-1656. Baulac M, Rosenow F et al. Efficacy, safety, and tolerability of lacosamide monotherapy versus controlled-release carbamazepine in patients with newly-diagnosed epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. <i>Lancet Neurol</i>, 2017;16(1):43-54 Reschke CR, ..., Rosenow F, Henshall DC. Potent Anti-seizure Effects of Locked Nucleic Acid Antagomirs Targeting miR-134 in Multiple Mouse and Rat Models of Epilepsy. <i>Mol Ther Nucleic Acids</i> 2017;6:45-56 Rajman M, ..., Rosenow F et al. A microRNA-129-5p/Rbfox crosstalk coordinates homeostatic downscaling of excitatory synapses. <i>The EMBO Journal</i> 2017 DOI 10.15252/embj.201695748 Johannesen K, ..., Rosenow F et al. Phenotypic spectrum of GABRA1: From generalized epilepsies to severe epileptic encephalopathies. <i>Neurology</i>, 2016;87(11):1140-51</p>

6.5. PROJECT PARTNER 5

Last Name	Kälviäinen
First Name	Reetta
Institution	University of Eastern Finland
Short CV	<p><u>Professional and University Career</u> Professor of Neurology/Clinical Epileptology, University of Eastern Finland, Kuopio, Finland, since 2010 Director, Epilepsy Center/NeuroCenter, Kuopio University Hospital Kuopio, Finland, which belongs to the European Reference Network for Rare and Complex Epilepsies EpiCARE, since 2007 Docent of Clinical Neurology, University of Kuopio, Finland, 1998 Specialist in Neurology, University of Kuopio, Finland, 1992 PhD in Medicine, University of Kuopio, Finland, Topic: “Prognosis of Epilepsy”, 1992 Licensed doctor, Finland (9.7.1986), ID number 256925 MD, 1986 University of Kuopio, Finland, 1985</p> <p><u>Grants</u> “Biomarkers of epilepsy”, which combines different methodologies (clinical, genetic, electrophysiological and imaging) to predict response and to better understand the interplay of epileptic activity and other pathophysiological processes of epilepsy, no overlap with the pre-proposal - Saastamoinen Foundation 2014–21 1,180,000 € - KUH special catchment area state research funding 2014–18 276,376 €</p> <p><u>Societal and scientific impact</u> Hirsch-index 42 (Web of Science), 12 articles cited more than 100 times, 132 published original scientific articles (128 international), 52 review articles (39 international), 32 book chapters, 2 editorials, editor of 2 books. Group member of 1 international and 1 European treatment guideline and 1 European White paper and Chair or group member in Finnish 6 treatment guidelines.</p>
List of five relevant publications within the last five years	<ol style="list-style-type: none"> 1. Brainstorm Consortium, ..., Depondt C, ..., Kälviäinen R et al. Analysis of shared heritability in common disorders of the brain. Science 2018;360, doi:10.1126/science.aap8757. 2. Kälviäinen R, Genton P, Andermann E, Andermann F, Magaudda A, Frucht SJ, Schlit A-F, Gerard D., Van Otterdijk E., de la Loge C., von Rosenstiel P. Brivaracetam in Unverricht-Lundborg disease: results from two randomized, double-blind, placebo-controlled studies. Epilepsia 2016;57:210-21. 3. Saavalainen T, Jutila L, Mervaala E, Kälviäinen R, Vanninen R, Immonen A. Temporal antero-inferior encephalocele: An under-recognized etiology of temporal lobe epilepsy? Neurology 2015;85:1467-74. 4. Huttunen J., Kurki M, Fraunberg M, Koivisto T, Ronkainen A, Rinne J, Jämskeläinen JE, Kälviäinen R, Immonen A. Epilepsy after aneurysmal subarachnoid hemorrhage in 876 patients – a population- based study. Neurology 2015;84:2229-37. 5. Hyppönen J, Äikiä M, Joensuu T, Julkunen P, Danner N, Koskenkorva P, Vanninen R, Lehesjoki A-E, Mervaala E, Kälviäinen R. Refining the phenotype of Unverricht-Lundborg disease (EPM1): a population-wide Finnish study. Neurology 2015; 84:1529-36.

6.6. PROJECT PARTNER 6

Last Name	Pandolfo
First Name	Massimo
Institution	Université Libre de Bruxelles
Short CV	<p><u>Professional and University Career</u> Chief of Neurology, Erasme Hospital, and Professor of Neurology, Brussels Free University (ULB), Brussels, Belgium, since 2001 Professeur Agrégé (Associate Professor), Université de Montréal, Department of Medicine, Montreal, Canada, 1996 – 2001 Adjunct Professor, McGill University, Department of Neurology and Neurosurgery, Montreal, Canada, since 1996 Assistant Professor of Neurology, Baylor College of Medicine, Houston, TX, 1994 – 1996 Assistente Medico di Neurologia (Assistant Professor), Division of Biochemistry and Genetics of the Nervous System, National Neurological Institute “C. Besta”, Milan, Italy, 1988 – 1993 Post-Doc in Molecular Genetics at University of California, Irvine, 1986 – 1988 Residency in Neurology at University of Milan, Italy, 1980 – 1984 Doctor in Medicine and Surgery (MD), University of Milan, Italy, 1980 Medical school at University of Milan, Italy, 1974 – 1980</p> <p><u>Grants</u> DEPDC5 in development and epilepsy: Supported by Belgian Fund for Scientific Research – Fund for Medical Scientific Research, 2016-18, 30,000€/year Deciphering oligo- to polygenic genetic architecture in brain developmental disorders: Supported by Concerted Research Action (ARC), French Community of Belgium, 2015-19, 120,000€/5 years Analysis of baseline and follow-up data from the EFACTS clinical cohort to develop potential end-points for a clinical trial in Friedreich’s ataxia: Supported by Voyager Therapeutics, 2016-18, \$100,000/year European Friedreich’s Ataxia Consortium for Translational Studies (EFACTS) - Support for the clinical network. Supported by Euroataxia, 2018-19, €106,000</p>
List of five relevant publications within the last five years	<p>225 publications, 19608 citations, H-index 69 (Google Scholar April 2018)</p> <ol style="list-style-type: none"> 1. Reetz K, Dogan I, Hilgers R-D, Giunti P, Mariotti C, Durr A, Boesch S, Klopstock T, Rodriguez de Rivera FJ, Schöls L, Klockgether T, Bürk K, Rai M, Pandolfo M, Schulz JB, on behalf of the EFACTS Study Group. Progression characteristics of the European Friedreich’s Ataxia Consortium for Translational Studies (EFACTS): a 2-year cohort study. <i>Lancet Neurology</i> 2016; 15:1346-1354. 2. Codazzi F, ..., Pandolfo M. Friedreich ataxia induced pluripotent stem cell-derived neurons show a cellular phenotype that is corrected by a benzamide HDAC inhibitor. <i>Hum Mol Genet</i> 2016;25:4847-55. 3. Hick* A, Wattenhofer-Donzé* M, Chintawar* S , ..., Pandolfo M#, Puccio HM#. Induced pluripotent stem cell derived neurons and cardiomyocytes as a model for mitochondrial defects in Friedreich's ataxia. <i>Dis Model Mech</i> 2013;6:608-631 (#shared last authors). 4. Kasperaviciute D, ..., Pandolfo M..., Reif PS, Rosenow F, ..., Depondt C et al. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. <i>Brain</i> 2013;136:3140-50 5. Dibbens LM, ..., Klein KM, ..., Pandolfo M et al. Mutations in DEPDC5 cause familial focal epilepsy with variable foci. <i>Nature Genet</i> 2013;45:546-51.

PROJECT PARTNER 7

Only in case of inclusion of partners from underrepresented countries. These partners must be eligible research groups from the following funding organisations: Canada (FRQS, CIHR), Croatia (MSE), Estonia (ETAg), Germany (Saxony), Italy (Lombardy, FRRB), Romania (UEFISCDI), Spain (GN), Spain (CDTI), Turkey (TUBITAK).

None

7. SIGNATURE

We are informed about the content of this proposal and we support its submission. To the best of our knowledge, we acknowledge that all contents are correct.

Project Consortium Coordinator

Family Name: Klein

First Name: Karl Martin

Institution: University of Calgary, Canada

Stamp and Signature

Karl Martin Klein

DEPARTMENT OF
CLINICAL NEUROSCIENCES

Date: 24 July 2018

Signatures of consortium partners:

Karl Martin Klein 24 July 2018

Klein, Karl Martin, University of Calgary, Canada

Colin Josephson

2018/07/20

Josephson, Colin, University of Calgary, Canada

Andreas G. Chiocchetti 18.07.18

Chiocchetti, Andreas G., Goethe-University Frankfurt, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Germany

Felix Rosenow 18.7.18

Rosenow, Felix, Goethe-University Frankfurt, Epilepsy Center, Germany

Reetta Kälviäinen 16.07.2018

Kälviäinen, Reetta, University of Eastern Finland, Kuopio University Hospital, Finland

Massimo Pandolfo

18.07.2018

Pandolfo, Massimo, Université Libre de Bruxelles, Hôpital Erasme, Brussels, Belgium



UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE

Office of the Dean
7th Floor, TRW Building
3280 Hospital Drive NW
Calgary, AB, Canada T2N 4Z6
T +1.403.220.6842
F +1.403.270.1828
E meddings@ucalgary.ca
cumming.ucalgary.ca

July 19, 2018

Dear Members of the Review Committee,

Re: Confirmation of Appointment for Karl Martin Klein

The Cumming School of Medicine (CSM, University of Calgary) is pleased to provide a letter confirming that Dr. Karl Klein has been given a Tenure Track appointment as an *Associate Professor* in the Departments of Clinical Neurosciences, Medical Genetics, and Community Health Sciences *effective September 1, 2018 – June 30, 2022*. To further support his research program, Dr. Klein will have 60% protected time for research which will be complemented by clinical duties (40%) at the Alberta Children's Hospital (ACH) and the Foothills Medical Center (FMC).

Yours sincerely,

A handwritten signature in blue ink, appearing to read 'Jon Meddings'.

Jon Meddings, MD, FRCPC, FCAHS
Dean, Cumming School of Medicine