Strategic Focus Area
Personalized Health and Related Technologies

3rd Call for Proposals for PHRT Supported Projects
Pioneer Projects: Multi "-OMICS" Data Collection and Interpretation of Clinical Sample Cohorts

In its 2017-2020 Strategic Plan for the ETH Domain, the ETH Board defined "Personalized Health and Related Technologies" (PHRT) as one of its Strategic Focus Areas. PHRT aims at contributing the scientific and technological strengths of the ETH Domain institutions to the field of personalized health and personalized health technologies. These contributions are seen as complementary to the efforts undertaken by other initiatives within the ETH Domain such as the Swiss Data Science Center (SDSC) and nationally, such as the Swiss Personalized Health Network (SPHN). An important goal of PHRT is to put ETH Domain institutions in a position to most fruitfully collaborate with clinical research partners, including those from SPHN and those from leading international programs. In addition, PHRT aims to develop synergies with the SDSC, e.g. through the development of computing infrastructure for managing and analyzing the large amounts of data required in personalized health, or by the development of high-performance computing/data science technologies focused on health-related research.

Following the 1st Call for proposals in 2017 and the 2nd Call for proposals in 2018, 51 PHRT projects were approved for funding. In parallel, two Technology Platforms (Health 2030 Genome Center in Geneva and the Proteomics Clinical Proteotype Analysis Center located in Zurich) have been established and are ready for the acquisition of **matched genomic, transcriptomic and proteomic data** from clinical cohort samples.

Generally, the platforms operate on a fee-for-service basis. However, to demonstrate feasibility of the platforms to generate high quality, coordinated and matched genomic, transcriptomic and proteomic datasets from large cohorts of clinical samples, PHRT has decided to financially support the data acquisition cost for a limited number of sample cohorts. The purpose of this call is to identify and select for funding such "Pioneer Projects".

In essence, Pioneer Projects shall bring together two parts, each of which has to offer ingredients that the other is lacking, a classical win-win situation.

Summary

PHRT is a program to achieve the goals stated by the ETH Board in the field of personalized medicine/health[1]. It intends to offer technological knowhow, expertise and capacity from the ETH Domain institutions to medical and clinical partners by supporting collaborative interdisciplinary research projects. With the present 3rd Call for proposals PHRT invites clinical scientists who have access to or have collected extensive high-quality sample cohorts in the context of a well-defined clinical question to request funding to generate matched genomic, transcriptomic and proteomic data in the respective PHRT platforms. Data processing, data integration, interpretation and data archiving shall be done by the applicants with assistance of PHRT platform IT scientists. Funding decisions will be based on peer review, under consideration of the criteria described below.

The ETH Board has ruled that PHRT funds generally can only be received from researchers of the ETH Domain and must be spent within ETH domain **research institutions,** with a few, well defined exceptions. Specifically, these exceptions these allow PHRT to cover costs for sample preparation or to compile clinical meta data and for the acquisition of matched genomic, transcriptomic and proteomic data from the respective clinical samples, even if the applicant is from outside the ETH domain. Procurement costs for the samples cannot be supported by PHRT.

The submission deadline for the proposals of the 3rd call is May 27, 2019.

[1] In this document the two terms “personalized health” and “personalized medicine” are used as interchangeable terms. Since the call is about clinical samples and not population samples, the term “**personalized medicine**” is used.

1 Introduction

The primary objective of personalized medicine is to recognize a human disease as a complex system and to achieve an integral and comprehensive understanding of this system at the molecular level to select optimized treatment for each individual. The study of disease systems in this framework generally requires interdisciplinary, inter-institutional cooperation between basic scientists, data scientists, clinicians and other disciplines.

Detailed description of the general goals, scope, mode of operation and project types of PHRT are found on the PHRT website at www.sfa-phrt.ch.

2 Description of Pioneer Projects

To address the need of typical personalized medicine projects to generate comprehensive, quantitative molecular profiles from clinical sample cohorts, PHRT has established two national platforms. The Health 2030 Genome Center is located in Geneva and supports genomic and transcriptomic analyses based on state-of-the art technology. The Clinical Proteotype Analysis Center is located in Zurich and supports quantitative proteotyping based on the SWATH/DIA technology. Both platforms have been extensively benchmarked and are operational.

Pioneer Project have been established to make the platforms immediately accessible to existing sample cohorts of high clinical significance. For approved Pioneer Projects PHRT bears the cost of data collection in the two platforms. It is expected that Pioneer Project proposals will be submitted by consortia of scientists. A consortium unifies documented expertise in medicine, clinical research and computational analysis of high dimensional data. Please note that both PHRT platforms have associated computational teams that offer their expertise.

Applicants are expected to submit a structured research proposal that addresses the specific issues described in the following. These issues will also guide the peer review committee. Since Pioneer Projects are intended to generate, in the near future, clinically relevant data from large sample cohorts, projects will only be considered if the sample sets are already available and approved or will reach that state within 3 months after the intended start date.

Please note that quality of the samples will be an important selection criterion. Platforms **cannot process blood plasma or FFPE samples** at this time point. The two platforms will support the applicants to clarify the suitability of their samples.

Applicants for a Pioneer Project are required to:

- provide a **clearly formulated clinical question** that is expected to be addressable with the data resulting from the project. Explorative studies without clear clinical focus are outside of scope.
- explain the aims of the project, **specific goals** and **clinical endpoints**.
- ensure that **consent for multi-omic experiments** has been given.
- provide **ethical approval** for all samples at time of application.

- document that a sample cohort achieving **statistical significance** is available at the time of application or within 3 months of the intended start date. As a guide, such studies typically include minimally 100 samples plus controls.
- demonstrate that the **samples are homogeneous**, of **high quality** and available at the start of the project or within 3 months of the intended start date.
- demonstrate the availability of **relevant clinical meta data** of the sample cohort to allow the association of the molecular profiles with clinical data.
- demonstrate that the **samples can be delivered** to the respective platforms within 3 months of positive funding decision.
- provide a **clear description** how the **high dimensional data** will be processed and used to gain new and relevant clinical knowledge
- provide a **plan for data management and ownership**
- provide a **detailed budget for the project**, using the fees per sample of the respective PHRT platforms as guidance.
- **clinical trials** can be included if they fulfil the criteria stated above.

For each Pioneer Project a single Principal Investigator (PI) is responsible for the submission of the proposal and, if approved for all scientific, technical and fiscal management tasks of the project, as well as for reporting. The PI does **not** need to be employed at an institution of the ETH domain. She/he is furthermore responsible the samples have the adequate consent for the project.

Please note:

- ➔ *PHRT does not pay for samples, just for processing the samples through the two platforms for the purpose of data collection.*
- ➔ *Funds for sequencing will be sent directly to the two platforms.*
- ➔ *The final project selection will be made by the Executive Committee of PHRT based on the opinion of external experts.*

3 Pioneer Project Boundary Conditions

The following conditions apply to the Pioneer Project Program.

Project duration	24 months
PHRT funding (max.)	CHF 500,000 per project to be used for sample processing, data acquisition on PHRT platforms, analysis (note: PHRT funding can only go to PHRT platforms and ETH Domain research groups) and for "clinical services" to prepare samples or compile clinical meta data (for hospitals, universities etc).
Number of approved projects with this call	up to 4
Full cost budget consists of different funding sources	a) funding requested from PHRT (sequencing, data analysis and clinical services). b) no matching funds from the university/university hospital partner institutions required. However, the institutions may allocate some internal resources since PHRT funds cannot go to these institutions (optional). c) funds directly linked to the project obtained from competitive research institutions such as SNSF, CTI, EU, NIH, etc to support further exploration of the generated data (optional). d) private funds: collaboration with partners from private industry and SMEs (optional).
Scope	Clinically relevant
Starting date	Oct 2019

Data ownership policy and authorship for publication

The PHRT Executive Committee strongly recommends to apply the following rules concerning data ownership:

- Data are generated on a fee-for-service basis and the platforms have, therefore, no claim form data ownership. Data ownership is with the PI and the research consortium. The centers will, however, retain the right to use data they generated, for the purposes of internal quality control and further development of their internal analytical workflows.
- At this stage of PHRT, platform personnel can be considered as co-authors of papers arising from the data, since it is not a commodity yet. However, general rules as defined e.g. by the SNSF or NIH author guidelines (see appendix) shall be applied.
- Data will need to be made publicly accessible through established data repositories after 6 months after collection or upon publication.

4 PHRT Technology Platforms

PHRT has established two platforms in Switzerland for large clinical sample cohorts, that generate consistent, high quality genomic, transcriptomic and proteomic data. Each platform has the capacity to process several thousand samples per year. Both platforms offer processing of primary digital data collected from the samples to the stage of quantitative profiles. The two platforms have developed elaborate and cutting-edge analytical tools for matched data analysis and interpretation of -omics data. To the degree that it is required and requested, the two platforms either individually or in collaboration can provide strong analytical solutions to the projects.

PHRT will pay sequencing costs directly to the two platforms. Approved funding for data analysis and clinical services (also for non ETH Domain institutions) will be paid out directly to the respective group.

4.1 The Health 2030 Genome Center, Campus Biotech in Geneva

The Center aims to provide for the large-scale sequencing needs of Switzerland, thereby facilitating genomic research and the implementation of genomic-based medicine. The Health 2030 Genome Centers mission is:

- to develop and deploy genomic technologies in support of research and clinical activities at the national and international levels
- to develop analytical tools and pipelines for genome analysis
- to serve as big data hub for the growing genomic needs of hospitals and research institutions
- to foster strong partnerships with existing private and public genomic platforms in Switzerland to ensure mutual exchange of know-how, experience and technology development
- to support public education in genomics and familiarize clinicians with genomic data

The Center offers the following sequencing and analytical services:

	Input material *	**Output**	**Price / sample**
RNA-seq (TruSeq Stranded mRNA-seq reagents)	High quality total RNA 100ng (minimum) 250ng (preferred)	50nt single read sequencing @ 25M PF clusters	**130 CHF**
		50nt paired end sequencing @ 25M PF clusters	**230 CHF**
Exome Sequencing (IDT xGen reagents)	High quality gDNA 300ng (determined by SYBR Green or equivalent)	70-fold mean coverage	**415 CHF**
		200-fold mean coverage	**750 CHF**
Genome Sequencing (PCR-free protocol)	High quality gDNA 1ug (determined by SYBR Green or equivalent)	30-fold mean coverage	**1200 CHF**

** Because of periodic updates in protocols and implementation, it is recommended to contact the platform before preparing the samples.*

	Input material *	Output	Price / sample
Other Genomic Assays, e.g. ChIP-seq, single-cell RNA-seq, DNA methylation analysis	Variable, depending on assay	Variable, depending on assay	**Variable, depending on assay**
	Analysis examples		
Data Analysis – 1st line analytics	Mapping, variant calling, data quality control, etc		Variable, depending on project
Data Analysis – 2nd line analytics	eQTL analysis, differential expression, variant annotation, etc		Variable, depending on project

** Because of periodic updates in protocols and implementation, it is recommended to contact the platform before preparing the samples.*

Team Health 2030 Genome Center:

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4.2 The Clinical Proteotype Analysis Center, ETH Zurich

The PHRT Clinical Proteotype Analysis Center is a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of disease/wellness, through the development and application of robust, quantitative, mass spectrometry-based strategies. The base technology of the platform is SWATH/DIA mass spectrometry,

The PHRT Clinical Proteotype Analysis Center provides knowhow, team, technologies, facilities and logistics to convert large sample cohorts of clinical specimens into digital representations of their molecular makeups (proteotypes) suitable, along with their clinical/phenotypic metadata, for further *in silico* research. Whereas the basic offering from the center consists of:

- Converting patients-derived peptide samples into quantitative protein matrices via a Data-Independent Acquisition (DIA) MS workflow and fast-track data analysis following SPHN Data Privacy and IT Security regulations
- Enabling shareability of the generated data within the PHRT/SPHN network according to the relevant data management guidelines as put forward by BioMedIT.

The center also provides assistance at all stages of a project on a collaborative basis, including

- experimental design, grant and manuscript preparation
- sample preparation for clinical proteotype analysis (cells, biofluids and tissues)
- deep track data analysis:
    - generation of more comprehensive spectral libraries (e.g. sample fractionation, pseudoDDA-based approaches, error-tolerant searches for the identification of post-translational modifications, …)
    - custom normalization / batch effect removal
    - proteogenomics analyses
    - machine learning based inference of signals of interest from the cohort proteotype
    - data visualization
    - and more generally custom data analysis workflows

The PHRT Clinical Proteotype Analysis Center operates on a full cost model for research & industry. Pricing includes standard sample preparation, spike-in standards, acquisition and fast track analysis. Additional analysis will be quoted/billed separately upon request.

Sample number	Academic pricing (CHF/sample)*	Industry pricing (CHF/sample)*
1-20	1000	3000
20-100	800	2400
100	600	1800

*Biospecimen requiring non-standard sample preparation will require a separate quote.

Team Clinical Proteotype Analysis:

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5 Scope of 3rd PHRT call for proposals

In the third call PHRT will support the generation of matched high-quality genomics, transcriptomics and proteomics data from clinical sample cohorts on the respective PHRT platforms (see Chapter 4).

A total of up to **CHF 1.5 million** is made available for funding three to four Pioneer Projects within the present call.

6 Documentation to be submitted

The PHRT Pioneer Project proposals are to be submitted using the official templates, which are available on the PHRT website, consisting of three parts:

Part 1: General information

Part 2: Scientific and technical information

a. Summary: concise statement of the goals, milestones and significance of the project (1-2 pages)
b. International standing of all applicants in their fields of research (max 2-3 pages in total)

c. Project plan (maximum 5 pages in total; CVs and references not included). **Note:** any pages exceeding 5 will not be considered).

c.1. Background and state of the art relevant to the project

c.2. Goals of the project: explanation of the clinical question(s) including relation to the clinical samples

c.3. Clinical samples: IRB (ethical) approval (consent for multi –omics research), number of samples (disease and control), state and quality of the samples, metadata, additionally available data and information, possibly required preparation to be sequenced by the two platforms
NOTE: Applicants are strongly recommended to contact as early as possible both platforms to clarify the suitability of their samples and strategies (**blood plasma or FFPE samples cannot** be analyzed the context of this pioneer grant since the focus is on matched genome, transcriptome and proteome data analysis).

c.4. Data management (integration/implementation), strategy of data processing

c.5. Description of the consortium, role of the main and each co-applicant

c.6. Expected impact and significance

c.7. Bibliography

- Attachments:
  - CV and publication list of the past 5 years of all main and co-applicants.
  - Potential reviewer (positive and negative list)
  - Link to SPHN or PHRT projects approved in 2017 and 2018: please explain the relation of the proposal to approved projects if there is any.

Part 3: Full cost budget (using the PHRT financial forms)

Adherence to the current valid version of the **Ethical Framework for Responsible Data Processing** is mandatory to apply for both PHRT and SPHN funding. Applicants should consult the PHRT webpage for information about the newest version of the Ethical Framework for Responsible Data Processing.

Submission Deadline

Pioneer Project proposals are to be submitted in PDF format by **May 27, 2019.** The proposal must sent to phrt-office@ethz.ch.

7 Selection criteria

The PHRT Executive Committee will evaluate the proposals according to the following criteria:

- Coherence of the proposal
- Experience and standing of the consortium members in their respective field
- Originality and feasibility of the goals and clinical question
- Availability and status of the clinical samples, metadata, etc
- Data management and processing
- Clinical relevance and implementation

The decision to grant projects will be based first of all on scientific criteria.

8 Selection procedure for PHRT proposals, time lines

Use of the official PHRT forms and completeness of the proposal, written in English. The selection of the proposals will be preceded by a formal check by the PHRT office. Proposals which fail to comply with the formal requirements will not be admitted to the next stage of the selection procedure and will be rejected if the defect cannot be easily remedied. The formal requirements must be met.

until	***action***	***by***
May 27	**deadline for submission** of the proposals	main-applicant
May 31	formal **check** and compliance with the required items	PHRT office
Aug 15	review by external and internal experts	reviewers
Sep 10	decision about approval and rejection	EC
Sep 30	information of the applicants	PHRT office
Dec 10	Latest start of the sequencing	PI

9 Annual scientific/technical and financial reporting

The annual scientific progress as well as financial reports of each PHRT project are to be submitted to the PHRT Office once a year. The reports will be consolidated and reviewed.

Financial and scientific reporting is to be provided according to defined directives.

Appendix: Data and Authorship Policy

Data

SNSF Guidelines on Open Research Data

FAIR Data Principles

Authorship in scientific publications

Analysis and recommendations of the Swiss Academies of Arts and Sciences

Scientific publications do not only serve the communication of science – the numbers of publications or of citations are essentially determining career opportunities of scientists. Accordingly, clear guidelines are needed that may help deciding who will be on the author list and in what order. The Scientific Integrity Committee of the Swiss Academies of Arts and Sciences has summarized prevailing regulations and formulated recommendations for authorship in scientific publications. These should help to prevent authorship disputes and offer guidance in the event of conflicts.