GET THE PICTURE: PIN1 PATHWAY AS A TARGET TO PREVENT CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

A Data Management Plan created using DMPonline.be

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Project abstract:

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare and underdiagnosed complication of pulmonary embolism (PE), characterized by fibro-thrombotic material mechanically obstructing large pulmonary arteries down to microvessels, aggravating PH, right ventricular failure and death, if left untreated. Today, surgical pulmonary endarterectomy, balloon pulmonary angioplasty and vasodilator drugs are used in combination, to confer near-cure in those with an early diagnosis. There is an unmet need to identify patients at risk developing CTEPH after acute PE. Peptidyl-Prolyl Cis/Trans Isomerase NIMA-Interacting protein 1 (Pin1) has pro-coagulant activity and its inhibition attenuates experimental PH in rats. Pin1 is elevated in plasma from CTEPH patients. Thus, we hypothesized that Pin1 could predict CTEPH after acute PE and its inhibition could be beneficial for the prevention of CTEPH. We consequently aim to investigate whether Pin1 is a discriminating biomarker to identify individuals at risk using large and unique cohorts of healthy subjects, acute PE and CTEPH patients. In addition, our goal is to explore whether inhibition of Pin1 could restore pulmonary vascular cell function in vitro using an organ on-a chip methodology and prevent CTEPH progression in vivo using a reliable CTEPH animal model coupled to imaging. The final goal is to translate our findings to the clinical practice to develop preventive therapeutic strategies to hinder CTEPH progression.

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FWO DMP (Flemish Standard DMP)

1. Research Data Summary

List and describe all datasets or research materials that you plan to generate/collect or reuse during your research project. For each dataset or data type (observational, experimental etc.), provide a short name & description (sufficient for yourself to know what data it is about), indicate whether the data are newly generated/collected or reused, digital or physical, also indicate the type of the data (the kind of content), its technical format (file extension), and an estimate of the upper limit of the volume of the data.

WP1

Origin/Source	Type	Format	Volumes
Informed consent form (Leuven)	Text	Printed paper	1 per patient
Human Plasma (Leuven)	Physical sample	Cryopreserved sample	2 samples per patient procedure
Overview sample collected	Text	.xlsx; OneNote	0.2 GB

WP2

Origin/Source	Type	Format	Volumes
Informed consent form	Text	Printed paper	1 per patient
Pulmonary endarterectomy (PEA) tissue	Physical samples	Human tissue	4-12 samples per patient
Swan-Ganz pulmonary arterial catheters	Physical samples	Catheter	1 catheter per patient procedure
Pulmonary arterial endothelial cells	Physical sample	Cryopreserved sample	2-3 samples per patient procedure
Overview sample collected	Text	xlsx	0.2 GB
Cell culture growth observation	images; text	.tiff; .xlsx	2 GB
Cell phenotyping	images; text	.tiff; .xlsx	5 GB
EVOS live imaging of pulmonary arterial endothelial cells	Movie	.mp4	10 GB
Angiogenesis data	images, raw data, graphs	.tiff; .xlsx; .pzf	5 GB
pulmonary arterial endothelial cell barrier function	images	.tiff; xlsx	0.3 GB
Protein lysates, RNA, cDNA	Physical sample	Cryopreserved sample	4-6 per patient
RNA, cDNA, qrtPCR	Molecular assessment	.txt; .xls; .png; .pdf; .pzf	1 GB
Paraffin embedded blocks from PEA material	Embedded tissue	Room temperature preserved sample tissue	4-12 blocks per patient
Cryoblocks from PEA material	Embedded tissue	Cryopreserved sample	4-12 blocks per patient
Histological images	Images	.vsi; .tiff	10 GB

WP4

Rabbits	Animals		40
Plasma	Physical sample	Cryopreserved sample	1-2 samples per animal procedure
Protein lysates, RNA, cDNA	Physical sample	Cryopreserved sample	4-6 per animal
Paraffin embedded blocks from rabbit tissue	Embedded tissue	Preserved sample tissue	4-12 blocks per animal
Cryoblocks from rabbit tissue	Embedded tissue	Cryopreserved sample	4-12 blocks per animal
Histological images	Images	.vsi; .tiff	10 GB
Telemetry data	Raw data, graphs	.pnm; .xlsx; .pzf	15 GB
Echocardiography data	digital, raw data, graphs	.dcm; .xlsx; .pzf	15 GB
microCT data	Digital data	.tiff	5 TB

If you reuse existing data, please specify the source, preferably by using a persistent identifier (e.g. DOI, Handle, URL etc.) per dataset or data type:

Not applicable

Are there any ethical issues concerning the creation and/or use of the data (e.g. experiments on humans or animals, dual use)? Describe these issues in the comment section. Please refer to specific datasets or data types when appropriate.

- Yes, human subject data
- Yes, animal data

Pulmonary vascular material and Swan-Ganz catheters are currently collected via the ethical approval S57114 and the biobank (S63978). Cellular composition and specific in vitro experiments will be addressed on pulmonary vascular endothelial cells isolated from pulmonary vascular material and Swan-Ganz catheters.

An ethical approval (P047/2022) related to the animal model has already been obtained for another project. A specific proposal related to the present project will be submitted to the local (KU Leuven) Ethical Committee for Animal Experimentation (ECD) within the second year (Q3-Q4) of the project.

Will you process personal data? If so, briefly describe the kind of personal data you will use in the comment section. Please refer to specific datasets or data types when appropriate.

- Yes

Personal data include demographic information (age, gender, length, body weight, home address...), medical information (hemodynamics, exercise capacity, echocardiography) and general health status (smoking behavior, pulmonary embolism history) and therapy (medical treatment). Data are exported from UZ Leuven medical record (‘KWS’). Marion Delcroix (promoter) and Rozenn Quarck (co-promoter) are responsible for data collection and management. These personal data are categorized as ‘special personal data’ of vulnerable individuals and will therefore be treated with caution.

Does your work have potential for commercial valorization (e.g. tech transfer, for example spin-offs, commercial exploitation, …)? If so, please comment per dataset or data type where appropriate.

- No

Do existing 3rd party agreements restrict exploitation or dissemination of the data you (re)use (e.g. Material/Data transfer agreements/ research collaboration agreements)? If so, please explain in the comment section to what data they relate and what restrictions are in place.

- Yes

Considering that the present project encompasses a collaboration with a non-KU Leuven partner (LUMC, Leiden, The Netherlands), agreements related to exploitation and dissemination have been written down in a collaboration agreement that will be signed by all parties involved in the project by September 2023.

Dissemination and exploitation of patient data to third parties obtained is restricted, and we will ensure privacy of the patients by pseudonymisation. A link between the patient and the dataset will be encoded. This code will not contain information that could lead to the identification of the patient and will be stored in an encrypted way on a different location than the pseudonymised data. The unique 'eenmalig administratief dossiernummer' (EAD number) in the UZ Leuven KWS patient database will not be used.Codes will only be accessible to Marion Delcroix, promoter and Rozenn Quarck, co-promoter.

Are there any other legal issues, such as intellectual property rights and ownership, to be managed related to the data you (re)use? If so, please explain in the comment section to what data they relate and which restrictions will be asserted.

- Yes

Considering that the present project encompasses a collaboration with a non-KU Leuven partner (LUMC, Leiden, The Netherlands), agreements related to exploitation and dissemination have been written down in a collaboration agreement that that will be signed by all parties involved in the project by September 2023.

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2. Documentation and Metadata

Clearly describe what approach will be followed to capture the accompanying information necessary to keep data understandable and usable, for yourself and others, now and in the future (e.g., in terms of documentation levels and types required, procedures used, Electronic Lab Notebooks, README.txt files, Codebook.tsv etc. where this information is recorded).

Standard experimental procedures (SOPs) and practices will be fully documented as word and PDF, and saved on GBW-0098_Pulmonary Circulation J-drive.

Those SOPs include:

- Pulmonary endarterectomy tissue collection and isolation pulmonary arterial endothelial cells
- Swan-Ganz catheter collection and isolation pulmonary arterial endothelial cells
- Blood collection and isolation of extracellular vesicles
- Culture procedures for pulmonary vascular endothelial cells
- Procedures to prepare the organ on-chip devices
- Procedures for in vitro assays (endothelium barrier function; angiogenesis)
- Sampling procedure and experimental protocol for live imaging, immunostaining, RNA studies and protein assays
- For microscopic image, dimensions, image type, bit-depth, pixel sizes and microscope settings will be noted and the methodology and protocol will also be described in details.
- Surgical and interventional procedures regarding the animal model (telemetry and catheter implantation, echocardiography, right heart catheterization, microCT).

Raw experimental data will be collected per experimental test, and will include a text file with a clear description of what the data represent and how they were generated.

This description will be documented in notebooks (with page numbers), in electronic format (word files) and/or in One Note.

The name of the folder will always contain the date, name of the experiment and the name of the person who performed the experiment.

Each individual file with experimental data will contain information on the study design, the origin of the samples, and all necessary information for an independent analyst to use or reuse the data accurately and efficiently.

Will a metadata standard be used to make it easier to find and reuse the data? If so, please specify (where appropriate per dataset or data type) which metadata standard will be used. If not, please specify (where appropriate per dataset or data type) which metadata will be created to make the data easier to find and reuse.

- Yes

For raw data, a meta datafile of the experimental settings will be created in a software-dependent format according to methodology. Metadata scheme using excel sheet with locked row and column will be used for other metadata related to experiments and will include data, name of the investigator, type of experiments and link to data documentation.

3. Data storage & back-up during the research project

Where will the data be stored?

Digital files of research data (raw data, figures, excel files, textual files, results from rabbit experiments etc.), that needs to be accessible daily and is exchangeable between KU Leuven-affiliated project participants will be stored on local KU Leuven researchers' PCs, and on the KU Leuven network editable drives, within which where the principal investigator has reserved dedicated space for this project (KU Leuven GBW-0098_Pulmonary Circulation J-drive).

Images from microCT and echocardiography, telemetry data or data that do not need to be frequently accessed will be saved on the shared KU Leuven GBW-0098_Pulmonary Circulation L-drive.

Paper lab notebooks will be kept in locked closets in the labs of the PIs.

Physical samples are stored in the laboratory in histology room, fridges, freezers (-20°C and -80°C), cryo-freezer (-150°C), depending on the kind of sample. At least one sample form all patient physical samples (pulmonary tissue, plasma sample) will be stored and archived in the UZ Leuven biobank.

A detailed overview list of all samples is available.

How will the data be backed up?

Researchers' computers are backed up through constant synchronization to the Enterprise Box cloud of the KU Leuven (which provides 100 Gb storage per KU Leuven researcher).

The KU Leuven network drives and the UZ Leuven central server are automatically backed-up on a daily basis.

Continuous KU Leuven network drive back-up is guaranteed and supervised by the KU Leuven ICT service and makes use of 'snapshot' technology.

Once data sets do no longer need to be accesses and/or modified, (e.g., after publication of manuscripts), archiving to a read-only KU Leuven network drive (the K drive) will be done to maintain a copy.

For the purpose of "business continuity" or "disaster recovery", a mirror (exact copy) of all data is created in a second datacenter where the data are copied every hour. In the event that the primary storage unit is corrupted, the ICTS team can get this copy online within an hour.

Back-ups from microCT and echocardiography images will be taken manually when images are collected.

Is there currently sufficient storage & backup capacity during the project? If yes, specify concisely.
If no or insufficient storage or backup capacities are available, then explain how this will be taken care of.

- Yes

Regarding digital data, each researcher will be given access to 100 Gb storage space on the KU Leuven Enterprise Box. For large volume datasets (e.g., microscopy images, microCT images, telemetry data), space will be reserved on the editable KU Leuven network drives (J or L). Space will be reserved on the read-only K drive for storage after the end of the project or after publication of manuscripts. Storage on the J and K KU Leuven network drives is extendable by blocks of 100 Gb, storage on the L drive is extendable per 5 Tb. Hence, by acquiring additional storage space based on the project's requirements, sufficient storage can be made available. For storage of physical data, sufficient storage space is available.

How will you ensure that the data are securely stored and not accessed or modified by unauthorized persons?

Digital data: The KU Leuven Enterprise Box cloud is suitable for secure storage of digital data non-personal data. Both UZ Leuven and KU Leuven network servers are compatible with GDPR regulations and allow for secure storage of personal data. The access to the KU Leuven server is u-number and password controlled. KU Leuven ICTS services provide the option to control data access for authorized persons only (in this case, KU Leuven affiliated research lab members involved in this project). As mentioned above for personal data stored on the UZ Leuven central server, access will be restricted with access right management only to clinical data manager Rozenn Quarck and by co-promoter Dr. M. Delcroix.

Access to the server and to "One Note" files is restricted to the research group members only and secured by a strict access right management controlled by the PI. The access to the KU Leuven server and One Note files is u-number and password controlled.

All physical data, printed forms and notebooks are stored in the labs in locked cabinet. Access to the lab is secured and badge

controlled. In case samples are stored at the Biobank, secure storage is guaranteed by controlling access to the storage location. Access to this location will be limited to one person and one back-up person per research group.

What are the expected costs for data storage and backup during the research project? How will these costs be covered?

Costs for **digital data** storage and back-up during the project have been included in the research budget of the project.
The current cost rate for the KU Leuven network drives are:
KU Leuven Enterprise Box: 25€/y/100 Gb block
J-drive: 503.66€/y/1 Tb block
K-drive: 6.40€/y/100Gb block (K),
L-drive: 869€/y/5Tb block.
Costs for **physical data** are only applying for biological samples of human origin in case they are stored in the Biobank. The UZ Leuven Biobank is currently still in the process of calculating the yearly storage cost per sample.

4. Data preservation after the end of the research project

Which data will be retained for at least five years (or longer, in agreement with other retention policies that are applicable) after the end of the project? In case some data cannot be preserved, clearly state the reasons for this (e.g. legal or contractual restrictions, storage/budget issues, institutional policies...).

All digital data and metadata will be retained for 10 years after the project (per the requirements of Research Data Management policy of the KU Leuven). The same term will be applied to physical data. Long-term storage of personal data additionally requires GDPR clearance, which will be obtained upon approval from the Ethics Committee of UZ Leuven.

Where will these data be archived (stored and curated for the long-term)?

Digital data will be archived on the KU Leuven K drive for storage of read-only data.

What are the expected costs for data preservation during the expected retention period? How will these costs be covered?

Cost rate for storage on the K drive is 6.4€/year/100Gb. To store a total of 5 Tb for 10 years, the estimated cost hence is 3,200 €. Costs will be allocated to the project budget.

5. Data sharing and reuse

Will the data (or part of the data) be made available for reuse after/during the project? In the comment section please explain per dataset or data type which data will be made available.

- Other, please specify:

Main findings of the research with all supporting processed data will be made available through publication in peer-reviewed journals with open access policies (as required by FWO regulations). All manuscripts will also be deposited in the KU Leuven Lirias digital repository.

If access is restricted, please specify who will be able to access the data and under what conditions.

All KU Leuven-affiliated researchers involved in the project will have access to non-personal data on the KU Leuven servers through their u-number and accompanying personal password. Since this project involves a collaboration with a third partner outside of KU Leuven (LUMC, Leiden, The Netherlands), data that can be shared will be deposited on a Teams-based storage platform that can be made accessible to external users.

Personal data will only be shared only with certain third parties (as will be specified in the GDPR addendum to the informed consent form) if needed, thereby always ensuring the privacy of the donors.

Are there any factors that restrict or prevent the sharing of (some of) the data (e.g. as defined in an agreement with a 3rd party, legal restrictions)? Please explain in the comment section per dataset or data type where appropriate.

- Yes, Other
- Yes, Privacy aspects
- Yes, Intellectual Property Rights

All KU Leuven-affiliated researchers involved in the project will have access to non-personal data on the KU Leuven servers through their u-number and accompanying personal password. Since this project involves a collaboration with a third partner outside of KU Leuven (LUMC, Leiden, The Netherlands), data that can be shared will be deposited on a Teams-based storage platform that can be made accessible to external users.

Since this project encompasses a collaboration with a non-KU Leuven partner (LUMC, Leiden, The Netherlands), agreements related to **exploitation and dissemination** have been written down in a collaboration agreement that will be signed by all parties involved in the project by September 2023.

Since this project encompasses a collaboration with a non-KU Leuven partner (Inserm, France), agreements related to**IP rights and ownership** have been written down in a collaboration agreement that will be signed by all parties involved in the project by September 2023.

Personal data will only be shared only with certain third parties (as will be specified in the GDPR addendum to the informed consent form) if needed, thereby always ensuring the privacy of the donors.

Where will the data be made available? If already known, please provide a repository per dataset or data type.

☐ In an Open Access repository
☐ In a restricted access repository
☒ Upon request by mail
☐ Other (specify):

When will the data be made available?

Data will be made available as publications at logical points during the course of the project when the research questions have been sufficiently addressed. Other data will be made available upon request, where considered appropriate, following publication.

Which data usage licenses are you going to provide? If none, please explain why.

All papers will be published in open access journals (according to FWO regulations) under an Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) license.

Do you intend to add a PID/DOI/accession number to your dataset(s)? If already available, you have the option to provide it in the comment section.

- No

What are the expected costs for data sharing? How will these costs be covered?

For sharing digital data, no sharing costs are foreseen. For sharing physical data, Material Transfer Agreements will have to be put in place which will be mutually signed. Shipping costs would be covered by either party (through the FWO budget in case of the provider) as long as the costs are low, however, significant sharing costs will be expected to be borne by the requestor.

6. Responsibilities

Who will manage data documentation and metadata during the research project?

The PI (Marion Delcroix) and Co-PI (Rozenn Quarck) will be responsible for documentation of data and metadata. PhD students and technicians will have the daily responsibility of record keeping of all data (digital, paper and biological samples). They will also be responsible for a correct and accurate data entry and recording of metadata.

Who will manage data storage and backup during the research project?

PhD students and technicians will have the daily responsibility of record keeping of all data (digital, paper and biological samples). They will also be responsible for a correct and accurate data entry and recording of metadata. The PI (Marion Delcroix) and Co-PI (Rozenn Quarck) will be responsible for data storage and back up during the project.

Who will manage data preservation and sharing?

Leuven: The PI (Marion Delcroix) and Co-PI (Rozenn Quarck).

Who will update and implement this DMP?

The PI (Marion Delcroix) and Co-PI (Rozenn Quarck).