DMP title

Project Name My plan (Internal Funds DMP) - DMP title

Grant Title C24M/21/041

Principal Investigator / Researcher FranÃ§ois Vermeulen

Project Data Contact els.aertgeerts@uzleuven.be

Description The study is a transitional project aiming to upscale the 'personalized medicine' approach to test modulator combinations or DNA based therapy for CF patients with rare mutations. The project is articulated in 3 work packages (WP), with parallel trajectories to reach the final objectives: 1. Personalized medicine for CF patients not eligible for registered modulator treatments - To screen for novel CFTR modulator combinations, both approved or in clinical development, to functionally rescue rare CFTR mutations for which the effect of approved modulators is unknown. Reached when 30 organoid samples from the KULeuven biobank are tested with CFTR modulators in 6 different combinations. (WP 1.1) - To develop novel tailored prime editing strategies for drug-refractory or non-druggable CFTR mutations. Mutations will be prioritized based on their prevalence and the availability in the organoid biobank, with priority to patient samples with two non-responsive mutations Reached when an allele-specific correction of the targeted CFTR mutations (n=7) is achieved on the genomic and functional level, with minimal off-target activity. For genotypes where the second allele is potentially rescuable by CFTR modulators, the best drug (or drug combination) for that specific mutation (obtained through the first objective) will be combined with the gene editing treatment to assess a potential additive effect. (WP1.2) 2. To develop and validate a novel microfluidic High-Throughput Screening (HTS) platform with increased test capacity on smaller organoid samples to allow rapid and in vitro drug HTS in a personalized medicine approach, as well as a phenotypically directed single organoid picking platform for downstream applications. Reached when (1) the results of the CFTR assay based on rectal organoids in wells can be replicated in the HTS platform in droplets (WP2) and (2) the microfluidic HTS platform has performed automated screening of 80 different combinations of modulators in organoids from 55 different patients and of gRNAs for gene editing in patients with selected non-druggable mutations (n=15), thereby establishing the capacity to perform HTS on a patient derived in vitro model (WP3) Research questions are mainly: - To which modulator(s) combination do rectal organoids of patients with rare CFTR mutations? - What are optimal guides for CRISPR/CAS correction of ultrarare 'non-druggable' mutations in rectal organoids - Can the CFTR assay in rectal organoids be applied in a microfluidic based platform system? - Can we test multiple modulator combinations or guide combination in a microfluidic based platform system? - Do results obtained in the high-throughput microfluidic platform system correlate with the results obtained in the low-trhoughput organoid assay?

Institution KU Leuven

1. General Information

Name of the project lead (PI)

François Vermeulen

Internal Funds Project number & title

C24M/21/041

Discovery Of Novel Therapies For Patients With CF Not Eligible For Registered Modulator Treatments, Assisted By Novel Microfluidic Techniques For Combinatorial, High-throughput Organoid Screens

2. Data description

2.1. Will you generate/collect new data and/or make use of existing data?

- Generate new data

2.2. What data will you collect, generate or reuse? Describe the origin, type and format of the data (per dataset) and its (estimated) volume. This may be easiest in a numbered list or table and per objective of the project.

WP	Partner (number, name)	Type of data	Format	Volume	How created	Ref in Text
WP1.1	P1 (FV)	microscopy	.tif	250GB	Confocal microscopy of organoid swelling after stimulation	A
WP1.2	P2 (MC)	microscopy	.czs .tif	1TB	Confocal microscopy of organoid swelling after stimulation	B
	P2 (MC)	sequencing	.abi	250GB	Genotyping of CRISPR	C
WP2.1	P3 (XC)	Automation routines	.exe (python, C++) .tif	1GB	AutoCAD	D
	P3 (XC)	CAD designs	.dwg	100GB	Written code	D
	P3 (XC)	Observational numerical data	.xls	1GB	Via a diversity of techniques	D
WP2.1	P3 (XC)	Code-supporting image sets	.tif .avi	100GB	LFI and microscopy	D
	P3(XC)	Droplet images	.tif .avi	1TB	LFI and microscopy	F
	P3(XC)	Organoid Images	.tif .avi	1TB	LFI and microscopy	G
WP3.1	P3(XC)	Organoid Images	.tif	250GB	LFI and microscopy	H
	P1(FV)	Microscopy	.tif	250GB	Confocal microscopy of organoid swelling after stimulation	I
WP3.2	P3(XC)	Organoid Images	.tif	250GB	LFI and microscopy	J
	P2(MC)	Sequencing	.abi	250GB	Genotyping after correction by CRISPR	K

3. Ethical and legal issues

3.1. Will you use personal data? If so, shortly describe the kind of personal data you will use. Add the reference to the file in KU Leuven's Record of Processing Activities. Be aware that registering the fact that you process personal data is a legal obligation.

Yes, we will use personal data:

Pseudonimized data:

- *CFTR* genotype

The project has approval of EC under S56329, including GDPR questionnaires.

Samples (rectal organoid cultures) are pseudonymized, no personal data reach the organoid lab. Personal subject data is stored in a pseudonymized Redcap database at UZ Leuven. The key to connect the subject identity to samples in the lab can be obtained from the PI.

3.2. Are there any ethical issues concerning the creation and/or use of the data (e.g. experiments on humans or animals, dual use)? If so, add the reference to the formal approval by the relevant ethical review committee(s).

Experiments on human tissues.

EC approval obtained (S56329)

3.3. Does your research possibly result in research data with potential for tech transfer and valorisation? Will IP restrictions be claimed for the data you created? If so, for what data and which restrictions will be asserted?

Our research has potential for tech transfer and valorization:

- application of CRISPR/CAS with improved guides
- application of the high throughput system to organoid based personalized medicine assays

3.4. Do existing 3rd party agreements restrict dissemination or exploitation of the data you (re)use? If so, to what data do they relate and what restrictions regarding reuse and sharing are in place?

No third-party agreements restricting dissemination are in place for any of the partners

4. Documentation and metadata

4.1. What documentation will be provided to enable understanding and reuse of the data collected/generated in this project?

P1,2,3 (FV, MC, XC)	microscopy	Images will be clearly labeled to identify experiment, sample, and date. Metadata concerning the technical specifications of the images (e.g. laser/gain/dimensions/etc) are collected with the .czi files, or else will be noted down by each experiment.
P1,2 (FV, MC)	Sequencing/genotyping	All files will be clearly labeled, to include experiment number and conditions. All experimental data will be noted every day in the lab book including all detailed experimental data. Once the sequencing data will be available, all files and folders will be labeled in a clearly structured way. The explanation of the labeling and the performed analysis will also be written down in the lab book and digital lab book (OneNote)
P1 (FV)	Biobank	P1 (FV) For the biopsy collection and cultures and storage of the organoids all the relevant info will be noted in a digital excel database. The methodology and protocols for isolation of crypts and culture and storage of the organoids will be described in detailed in the lab book. For the biopsy collection the following info will be noted: label of the sample (pseudonymized ID), origin of the samples (centre), data of collection/extraction, number of biopsies, number of wells platted after isolation protocol and operator. For the organoid culture the following info will be noted: ID of sample, passage number, data of passage, plan for the sample. For the organoid samples the following info will be noted: ID of the samples, data of storage, number of wells stored per cryovials, passage number when stored and operator.

4.2. Will a metadata standard be used? If so, describe in detail which standard will be used. If not, state in detail which metadata will be created to make the data easy/easier to find and reuse.

No specific metadata will be generated.

The use of metadata standards has not been implemented in the daily routine of the research group. In case this will change in the course of the project this change and its timing will be reported at the end of the project.

The lab codebook will contain all information on which samples from the biobank were used for which experiments, to allow back tracability to inform patient and physicians.

5. Data storage and backup during the project

5.1. Where will the data be stored?

Time-stamped master copies of all data will be stored centrally (M.Carlon and CF organoid research group at SCIL, X.Casadevall at own research lab and KUL servers). Personnel involved in

the project will use different types of data storage and reporting: **(1)** A physical lab book with the chronological reporting of all related experiments and results including a cross reference to electronic storage of data. These lab books are owned by the research group and remain in the laboratory during the entire time. Finalized lab books are stored in the lab archives for at least 10 years. **(2)** Electronic lab books (OneNote) for which all entries (including changes) are recorded. **(3)** Large data set, such as images from microscopy are stored on the KU Leuven L drive (large storage server-MC) or on the private computer attached to the microscope (20TB) and daily backup to an external drive (5T) (permanently connected to the computer using toolkit software for automatic backup (FV). In addition, the members of the laboratory use the OneDrive for daily backup of all personal folders.

5.2. How will the data be backed up?

Time-stamped master copies of all data will be stored centrally (M.Carlon lab and CF organoid research group at SCIL). Personnel involved in will use different types of data storage and reporting: **(1)** A physical lab book with the chronological reporting of all related experiments and results including a cross reference to electronic storage of data. These lab books are owned by the research group and remain in the laboratory during the entire time. Finalized lab books are stored in the lab archives for at least 10 years. **(2)** Electronic lab books (OneNote) for which all entries (including changes) are recorded. **(3)** Large data set, such as images from microscopy are stored on the KU Leuven L drive (large storage server) or on the private computer attached to the microscope (20TB) and daily backup to an external drive (5T) (permanently connected to the computer using toolkit software for automatic backup. In addition, the members of the laboratory use the OneDrive for daily backup of all personal folders.

5.3. 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.

The OneDrive does have limitation in storage capacity (2TB) and provides periodic backups. For large data the laboratory has an external drive with a 5TB storage capacity which when full can be substituted by another external drive if necessary. The drive is kept in a locked location at the Orgnaoid lab.

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

Expected costs for data storage are covered by research grants in the labs of the 3 partners

5.5. Data security: how will you ensure that the data are securely stored and not accessed or modified by unauthorized persons?

All data will be retained for at least 10 years after the project. Thus, complying to the data preservation rules of KU Leuven.

6. Data preservation after the end of the project

6.1. Which data will be retained for the expected 10 year period after the end of the project? If only a selection of the data can/will be preserved, clearly state why this is the case (legal or contractual restrictions, physical preservation issues, ...).

All data will be retained for at least 10 years after the project. Thus, complying to the data preservation rules of KU Leuven.

6.2. Where will these data be archived (= stored for the long term)?

Each research group will maintain the backups on the servers. After the end of the project, data may be maintained on the servers or on hard drives kept in secured places in each lab.

6.3. What are the expected costs for data preservation during these 10 years? How will the costs be covered?

Cost of the preservation will depend on volume of data and method of preservation. Storage on servers is structurally financed in each research group.

7. Data sharing and re-use

7.1. Are there any factors restricting or preventing the sharing of (some of) the data (e.g. as defined in an agreement with a 3rd party, legal restrictions or because of IP potential)?

All data will be generated by the research groups involved, without restrictions for future use within the scope of the present project.

7.2. Which data will be made available after the end of the project?

Data with valuable IP will be protected prior to publication. We will strive to comply with open access guidelines at KU Leuven and therefore relevant digital data will be published and made available after the end of the project via public repositories (e.g. zenon-do.org).

Anonimized example datasets and images will be made available.

7.3. Where/how will the data be made available for reuse?

- Upon request by mail

Data will be available after signing a data sharing agreement which will be established with the support of KUL R&D after a request. Once KU Leuven has established a university managed and owned data repository sharing of data (or a subset of data) on this repository will be evaluated depending on the policy and conditions of this repository. Changes to the data sharing policy will be reported in the final DMP.

7.4. When will the data be made available?

- Upon publication of the research results

Data will be made available after publication in peer reviewed journals. Additional data will be made available on basis of data sharing agreements if requested by third party. The anonymized data could be made available upon publication of the results, only if anonimization can be guaranteed (given ultra-rare mutationsin many patients)

7.5. Who will be able to access the data and under what conditions?

Due to the potential commercial value of data no general and full open access to data will be provided by default. Data which will be shared with third parties will exclude commercial use and will require appropriate credit to the data owners.

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

No data sharing is actually planned.

The KU Leuven repository will not request any cost contribution for KU Leuven researchers. Data shared through journal repositories will be covered by publication costs. Bilateral agreements for data sharing will be established through the services of KU Leuven R&D. The costs expected for data sharing are thus low and will be reported in the final DMP at the end of the project. They will be covered through funds of the project.

8. Responsibilities

8.1. Who will be responsible for the data documentation & metadata?

The individual researcher producing data will have the final responsibility for data documentation and metadata. In case of PhD students and technical personal the collection will be supervised by the scientific project responsible (Dr. Marianne Carlon, Dr. Anabella Ramalho and Dr. François Vermeulen, Dr Xevi Casadevall) while remaining the final responsibility of data integrity by the researcher performing the experiments.

8.2. Who will be responsible for data storage & back up during the project?

Data storage and back-up underlies the responsibility of the individual researcher, who will be supervised by the scientific coordinator. The responsibility for maintaining the infrastructure access for data storage lies in the hands of the IT responsible of the research team. Finally, the maintenance of servers and integrity of data stored on these servers underlies the ITC services of the university. The maintenance of the integrity of the external drives and the data stored on them will be responsibility of the lab manager (FV).

8.3. Who will be responsible for ensuring data preservation and sharing?

Prof François Vermeulen will take responsibility to ensure data preservation, access and reuse. Each partner will take care of data preservation for his/her tasks of the project.

8.4. Who bears the end responsibility for updating & implementing this DMP?

The end responsibility for updating and implementing the DMP is with the supervisor (promotor)

François Vermeulen.