NEURO-IMMUNE MECHANISMS OF VISCERAL HYPERSENSITIVITY

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Funder: KU Leuven (KUL)

Template: KU Leuven BOF-IOF

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Grant number / URL: ZKE4255 C14/23/134

ID: 206184

Start date: 01-10-2023

End date: 30-09-2027

Project abstract:

Irritable bowel syndrome (IBS) is one of the most prevalent gastrointestinal disorders with a prevalence of 4-10% worldwide. Mainly due to a limited insight in its pathophysiology, treatment is currently rather disappointing. In the present project, we aim to discover the underlying mechanism(s) responsible for abnormal pain signaling in patients with IBS. We will search for novel therapeutic targets based on recently completed single cell RNA sequencing experiments of IBS rectal biopsies and murine isolated dorsal root ganglia (DRG) neurons of hypersensitive animals. In addition, we will investigate the role and molecular determinants of membrane potential instabilities, a mechanism that we recently found to regulate action potential firing in sensory neurons. The outcome of this project will lead to increased insight in the pathophysiology of IBS and ultimately to improved clinical management of this debilitating disorder.

Last modified: 04-04-2024

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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.

Dataset name / ID	Description	New or reuse	Digital or Physical data	Data Type	File format	Data volume	Physical volume
MRGPRX2 in colon/rectum mast cells-IHC (WP1.1a)	Immunostaining images of MRGPRX2 in mast cells from control hemicolectomy patients and rectal biopsies of HV and IBS	N	D	I, T	.czi, .jpg, .xlsx, pzfx	<100Gb	NA
MRGPRX2 in mast cells from colon layers-RNA (WP1.1b)	RNA expression of MRGPRX2 in FACS-sorted mast cells sorted from mucosa, submucosa, and muscularis of colon tissue from control hemicolectomy patients	N	D	T	.fcs, .jo, .csv, .xlsx, .pzfx	<1Gb	NA
MRGPRX2 in rectal biopsies-FC (WP1.1c)	MRGPRX2 expression in rectal biopsies	N	D	I, T	.fcs, .jo, .exdat, .xslx, .pzfx	<100Gb	NA
Questionnaires (WP1.1d)	Observational data from patient files	N	D	T	.sav, .csv	<1Gb	NA
Biopsy supernatant MRGPRX2 activity (WP1.1e)	MRGPRX2 CHO cell calcium imaging	N	D	T, I	.tif, .vws, .csv, .pzfx	<1Tb	NA
Mast cell degranulation and neuronal sensitization (WP1.1f)	Live imaging of mast cell degranulation and sensitization of TRPV1 submucosal neurons in response to MRGPRX2 agonist	N	D	A, I, T	.czi, .jpg, .xlsx, pzfx	<1Tb	NA
Mrgprb2-null visceral pain after WAS-IBS (WP1.2a)	VMR data of Mrgprb2-null mice after sham/WAS-IBS	N	D	T	.txt, .csv	<10Gb	NA
MRGPRX2 agonists in murine colon supernatant after WAS-IBS (WP1.2b)	ELISA of MRGPRX2 agonists in murine colon supernatant after sham/WAS-IBS	N	D	T	.txt, .csv, .xlsx, .pzfx	<1Gb	NA
scRNASeq mast cells colon layers (WP2.1)	scRNASeq dataset from colon immune cells from the mucosa, submucosa, muscularis of control hemicolectomy patients	N	D	Omics datasets	.loom, .h5ad	<1 Tb	NA
Spatial validation of mast cell targets (WP2.2a)	HCR-RNA FISH or MERFISH on rectal biopsies	N	D	Omics datasets	.gif, .jpeg, .tiff, .cloupe, .json	<1 Tb	NA
In vitro mast cell validation (WP2.2b)	KO and control in vitro differentiated mast cells, phenotypical and functional observations	N	D	I, T	.txt, .fcs, .jo, .exdat, .czi, .xlsx, .csv, .pzfx	<100Gb	NA
SMARTSeq2 DRG (WP3.1)	scRNASeq of murine colon-innervating DRG neurons	N	D	Omics datasets	.loom, .h5ad	<1 Tb	NA
Spatial validation of DRG targets (WP3.2a)	HCR-RNA FISH or MERFISH on murine DRG	N	D	Omics datasets	.gif, .jpeg, .tiff, .cloupe, .json	<100Gb	NA
DRG-KO mice neuronal excitability after PI-IBS (WP3.2b)	Patch clamp on target gene-KO in murine DRG	N	D	T, A	.txt, .abf, .atf, .csv	<100Gb	NA
DRG macrophages after PI-IBS (WP4.1a)	Flow cytometry and IHC data, macrophages in murine DRGs after PI-IBS	N	D	I, T	.fcs, .jo, .csv, .czi, .jpg, .xlsx, pzfx	<100Gb	NA
scRNASeq macrophages in DRG after PI-IBS (WP4.1b)	scRNASeq of macrophages from murine colon-innervating DRG after PI-IBS	N	D	Omics dataset	.loom, .h5ad	<1 Tb	NA

Validation of macrophage targets 'WP4.1c)	Spatial transcriptomics and MILAN on murine DRG	N	D	Omics dataset	.gif, .jpeg, .tiff, .cloupe, .json, .czi, .jpg, .xlsx, pzfx	<100Gb	NA
Mph-KO mice neuronal excitability after PI-IBS (WP4.2a)	Patch clamp on Mph-depleted mice after PI-IBS	N	D	T, A	.txt, .abf, .atf, .csv	<100Gb	NA
Mph-KO mice neuronal excitability after PI-IBS (WP4.2b)	Flow cytometry data and IHC in murine DRGs depleted of Mph after PI-IBS	N	D	I, T	.fcs, .jo, .csv, .czi, .jpg, .xlsx, pzfx	<100Gb	NA
Membrane potential instabilities in VHS (WP5)	Patch clamp on DRG neurons from control VHS mice and in genetically altered VHS mice	N	D	T, A	.txt, .abf, .atf, .csv	<2Tb	NA

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:

N/A

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, refer to specific datasets or data types when appropriate and provide the relevant ethical approval number.

- Yes, animal data (Provide ECD reference number below)

Human subject data: S55484, S62059, S51573
Animal data: 022/2024

Will you process personal data? If so, please refer to specific datasets or data types when appropriate and provide the KU Leuven or UZ Leuven privacy register number (G or S number).

- Yes (Provide PRET G-number or EC S-number below)

Patient samples/information (biopsies, faeces, blood, questionnaires). Human subject data: S55484, S62059, S51573

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.

- Yes

The major aim of the present project is to obtain more insight in the pathophysiology of IBS with the ultimate goal to discover novel therapeutic targets. Discoveries will be patented following consultation of and close interaction with LRD. Concerns: mast cell gene targets, DRG gene targets, macrophage gene targets.
Our models and know-how will be of interest for industrial partners, such as Takeda, Eli Lily, Viatris, and GSK, leading to new contracts and further valorisation of our research. Concerns IBs models (PI-IBS, WAS-IBS), abdominal pain measurement (VMR), pain sensitivity (patch-clamp).

Do existing 3rd party agreements restrict exploitation or dissemination of the data you (re)use (e.g. Material or 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.

- No

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.

- No

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).

Each experiment is registered in the lab journal of the scientist performing the respective experiment. Standard operation procedures (SOPs) have been written for all the techniques used in the lab. Data obtained from a study protocol / series of experiments will be stored in a folder that also contains a readme.txt file explaining the design/protocol, results and labels used in the data analysis file, and a reference to the lab journal of that particular experiment. Also the method of analysis will be described. The information provided will allow another researcher to follow all steps in the data processing.

Will a metadata standard be used to make it easier to find and reuse the data?
If so, please specify which metadata standard will be used.

If not, please specify which metadata will be created to make the data easier to find and reuse.

- Yes

Metadata will be created for the transcriptomics using the Dublin core (http://www.dcc.ac.uk/resources/metadata-standards/dublin-core).
Flow cytometry metadata will be generated as part of the Flow Cytometry Standard data file, according to the ISAC standards (https://isac-net.org/page/Data-Standards).
Microscopic metadata will be generated using the OME-TIFF or OXE-XML standard (www.fairsharing.org).
Other metastandard are not available yet (http://www.dcc.ac.uk/resources/metadatastandardsOR http://rd-alliance.github.io/metadatadirectory/standards/OR https://fairsharing.org/).
In these cases, metadata will be included in the read-me file, including description of equipment and settings used and experimental conditions.

Data Storage & Back-up during the Research Project

Where will the data be stored?

- ManGO
- Shared network drive (J-drive)
- OneDrive (KU Leuven)
- Large Volume Storage

How will the data be backed up?

- Standard back-up provided by KU Leuven ICTS for my storage solution

Is there currently sufficient storage & backup capacity during the project?

If no or insufficient storage or backup capacities are available, explain how this will be taken care of.

- Yes

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

Data files are stored on the J drive of KU Leuven which is protected via a central login for KUL personnel. Identity of included patients is encoded, i.e. a unique number (hospital patient number) coupled to a unique CRF (case report form) number.
The file containing the link between the CRF number and the patient's identity is saved in a dedicated folder on the J drive which is only accessible by the PI and trial nurse via an entrance code. In case data are stored on managed laptops, the hard drive is encrypted.

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

The extra costs approximate 160 euro per TB/year (per blocks of 5 TB). The costs will be paid from this project.
The freezers to store tissue samples are purchased by the different PIs and located in the UZ Leuven biobank at no cost. The costs of a -80°C freezer is around 3000-5000 euro.

Data Preservation after the end of the Research Project

Which data will be retained for 10 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 data will be preserved for 10 years according to KU Leuven RDM policy
- Certain data cannot be kept for 10 years (explain below)

Remaining physical pertaining to the previously described datasets cannot be kept for 10 years as their integrity degrades with time. Those samples will likely be kept for 5 years after they have been collected, after which they will not longer be useable.

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

- Other (specify below)

KU Leuven K Drive. Permission to access the K drive is limited to the PI and only for read-only use. Archived data may no longer be modified..

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

The estimated amount of data (scRNAseq data excluded) can be stored on the K drive, KU Leuven ICTS. If needed, an upgrade will be requested at 156,60 euro/TB/year. The expected maximum data volume of 2 TB will cost a total of 3200€ for 10 years (2 x160 euro/yr x 10 years). The costs will be paid from the current project.

Data Sharing and Reuse

Will the data (or part of the data) be made available for reuse after/during the project?

Please explain per dataset or data type which data will be made available.

- Other (specify below)

Data that are not under IP will be made available after the end of the project.

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

Data that are not under IP will be made available after the end of the project, as described below.

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 per dataset or data type where appropriate.

- Yes, privacy aspects

Where will the data be made available?

If already known, please provide a repository per dataset or data type.

- Other (specify below)

Data will be shared within the research unit.
Data under IP will not be shared with peers. Sequencing data will be uploaded to an open access repository and shared upon request. The data will be protected by creative commons.
Data without sharing restrictions will be shared through peer reviewed publications.

When will the data be made available?

- Upon publication of research results

The data will be made available after publications via the required link in the publication or upon request.

Which data usage licenses are you going to provide?

If none, please explain why.

- CC-BY 4.0 (data)

Do you intend to add a persistent identifier (PID) to your dataset(s), e.g. a DOI or accession number? If already available, please provide it here.

- Yes, a PID will be added upon deposit in a data repository

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

Peers can use the data at no cost under the condition of co-authorship. Commercial organizations will have to pay a fee that will be determined by LRD-KU Leuven.

Responsibilities

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

G. Boeckxstaens

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

A person within the lab will be responsible for the data storage.

Who will manage data preservation and sharing?

G. Boeckxstaens

Who will update and implement this DMP?

The PI bears the end responsibility of updating & implementing this DMP.