Tricking tumor immunosuppression: RNA epigenetics as novel target to improve cancer immunotherapy

A Data Management Plan created using DMPonline.be

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Project abstract:

RNA epigenetics is a recently discovered additional layer of epigenetic control of the cellular phenotype, besides histone modifications and DNA modifications. Some RNA modifications (m6A, wobble uridine 34 tRNA) were reported by members of this consortium and others to influence cancer cell behavior and therapy resistance, in a cancer cell-intrinsic fashion. However, RNA modifications are also known to modulate immune cell functions. Since immune cells are an integral part of the TME, which may strongly affect tumor progression and metastasis, a better knowledge of their RNA epigenome is warranted to improve cancer immunotherapies.

This is especially true for macrophages, whose functions are mostly skewed towards tumor promotion and immunosuppression. These cells are, hence, considered as novel frontier cancer therapeutic targets, especially in combination with the current arsenal of immunotherapeutics. RNA modifications were reported to influence macrophage differentiation, activation and function, with sparse information being available on TAMs (only for m6A). However, **a comprehensive overview of which RNA modifications are influencing the TAM phenotype is currently lacking. Moreover, no information is available about differential RNA modifications in TAM populations that are affected by distinct tumor microenvironmental cues, such as hypoxia, acidosis, and nutrient shortage. We, therefore, aim to investigate whether distinct TAM subsets, exerting different functions in the TME, are differentially regulated by novel RNA epigenetic mechanisms.**

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Application DMP

Questionnaire

Describe the datatypes (surveys, sequences, manuscripts, objects …) the research will collect and/or generate and /or (re)use. (use up to 700 characters)

We will generate new data from mouse models and human clinical samples, more specifically data from single-cell RNA-sequencing, spatial transcriptomics, CITE-Seq, epigenetics, microscopy, flow cytometry, nucleotide sequences, and ELISA, as well as phagocytosis, cytotoxicity, antigen presentation, T-cell suppression assays.
Lentiviral vectors, engineered cell lines, and transgenic mouse strains will be constructed.
Research documentation (data analysis, standard operating procedures, ethical approvals) is kept in a lab book and in electronic formats including Graphpad Prizm, MS Excel, MS Word, and Adobe Portable Document Format.
We also aim to compile manuscripts (research articles and reviews).

Specify in which way the following provisions are in place in order to preserve the data during and at least 5 years after the end of the research? Motivate your answer. (use up to 700 characters)

Massimiliano Mazzone, Jo Van Ginderachter, François Fuks, and Pierre Close will be responsible for the storage and preservation of data generated in their respective groups.
The different partner institutes (KULeuven, VUB, ULB, and ULiège) have sufficient and scalable storage capacity available, both during the research and at least 5 years after the end of the research. Data storage and backup is based on a combination of internal servers and external storage with commercial providers such as Microsoft and with public databases and repositories. Non-public data are login-protected and accessible to designated staff members only.

What’s the reason why you wish to deviate from the principle of preservation of data and of the minimum preservation term of 5 years? (max. 700 characters)

As a general rule, data will be preserved for a minimum term of 5 years. Datasets collected in the context of clinical research, which fall under the scope of the Belgian Law of 7 May 2004, will be archived for 25 years, in agreement with the University Hospitals policies and the European Regulation 536/2014 on clinical trials of medicinal products for human use

Are there issues concerning research data indicated in the ethics questionnaire of this application form? Which specific security measures do those data require? (use up to 700 characters)

All experiments on mice and on human clinical samples are conducted according to institutional, national, and European regulations. Work with laboratory animals that are not yet included in ongoing approvals will be subjected to prior formal approval by the Ethical Committee on Animal Experimentation of the respective institutes before the start of the respective work packages.
Work on human biological material will be subjected to approval by the respective Ethics Committee.

Which other issues related to the data management are relevant to mention? (use up to 700 characters)

We do not exclude that the proposed work could result in research data with the potential for tech transfer and valorization. The partner institutes have a policy to actively monitor research data for such potential. If there is substantial potential, the invention will be thoroughly assessed, and in a number of cases, the invention will be IP-protected (mostly patent protection or copyright protection). As such the IP protection does not withhold the research data from being made public. In the case a decision is taken to file a patent application it will be planned so that any delay to publication is minimal.

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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.

Dataset Name	Description	New or reused	Digital or Physical	Digital Data Type	Digital Data format	Digital data volume (MB/GB/TB)	Physical volume
	scRNA-seq	New	digital	experimental	.bam	<10TB	
	Flow cytometry	New	digital	experimental	.fcs	<5TB	
	Microscopy	New	digital	experimental	.lsm .tiff	<1TB	
	Phagocytosis Cytotoxicity Antigen presentation T cell suppression	New	digital	experimental	.xlsx .pfz .fcs	<1GB	
	SOPs	New	digital	experimental	.pdf	<1GB	
	RT-qPCR	New	digital	experimental	.xlsx .pfz	<1Gb	
	Metabolomics	New	digital	experimental	.raw .pmd	<10GB	
	Lipidomic	New	digital	experimental		<5TB	
	Tumour growth, volume, metastasis	New	digital	experimental	.xlsx .pfz	<1GB	
	Histology	New	digital	experimental	.lsm .tiff	<1TB	
	Angiogenic sprouting, invasion, tube formation	New	digital	experimental	.tiff .xlsx .pfz	<10GB	
	Illustrations	New	digital	experimental	.ai .pdf .tiff	<5GB	
	pubblication	New	digital	experimental	.pdf	<5GB	
	Murine organ	New	physical				10 boxes
	Lentiviral vectors	New	physical				5 boxes
	Mouse strains	New					

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:

NA

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

All animal experiments to be performed have been approved or submitted to the Ethical Committee for Animal Experimentation (ECD) at KU Leuven (Projects P194/2022 P060/2021)
Work on human clinical samples is conducted according to institutional, national, and European regulations. In this case, the work performed falls under the umbrella of the MIMIPAC clinical trial (MEDI4736, UZ reference S61508).

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.

- No

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

Intellectual property arising from this work will be managed based on the framework agreement between VIB (VIB Tech Transfer) and KU Leuven.

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.

- 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

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).

Protocols and details related to data collection and processing will be recorded in physical lab books and transcribed to Word or Excel files by the applicants. Long-term storage of the lab books is supervised by the lab manager. The lab book describes in detail the experimental setting and any deviation from the original experimental design. Experiments are organized by date and therefore fully searchable. Data folders containing raw and processed data will be hierarchically organized and labeled based on the source of the data, the type of experiment, the date of data generation, and the different experimental conditions analyzed. Data analysis methods and particularities (including metadata) will be described in text documents and Excel files included in these folders. Standard operating procedures (SOP) are constantly updated and safely stored as PDFs to ensure proper replication of biological experiments. SOPs are backed up to the J-drive once per month, where they are available for all members of the lab. Similarly, all the experimental data (raw and processed data), are safely stored in dedicated drives.

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.

- No

Text documents and Excel files stored within each experiment folder will respectively contain guidelines describing data collection/analysis methods and all relevant metadata (including experimental conditions, sample keys, computational analysis pipelines, and their parameters) to ensure the reusability of the data and the reproducibility of any further data generation. Experiments are organized by date so they can be compared with lab books for additional information. References of reagents used are listed on an Excel table together with the reference and the dilution used.

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

Where will the data be stored?

Storage options: (1) J-Drive (Minimum 100Gb, Expandable, Unlimited Size, Stored data can be modified); (2) L-Drive (Minimum 5Tb, Unlimited Size, Stored data can be modified); (3) K- Drive (Archive storage, Minimum 100Gb, Expandable, Unlimited Size, Stored data can NOT be modified or deleted).

How will the data be backed up?

Data storage and backup is managed by KU Leuven IT services. Specifically, mirror copies of the stored data are made immediately upon upload, for safety backup purposes. Data storage and backup is based on a combination of internal servers and external storage with commercial providers such as Microsoft, and with public databases and repositories. Long-term storage is ensured by the L-drive (stored data can NOT be modified or deleted. This will guarantee the preservation of data over a minimum term of 10 years. Regular computer backups through the inSync platform (unlimited storage) secure the recovery of unsaved data.

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

The institutes (KU Leuven and VIB) have sufficient and scalable storage capacity available, both during the research and during at least 10 years after the end of the research.

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

Non-public data are login-protected (2FA) and accessible to designated staff members only. Network security is ensured by the KULeuven IT services.

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

The annual cost of storage is approximately 569.2 € per 5TB of storage space per year. This cost and capacity include the performance of mirror copies of the stored data, for safety backup purposes. These costs will be covered by the budget of the project leader.

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...).

Biologicals will be retained when possible. The storage will be at (1) room temperature, (2) 4°C, (3) -20°C, (4) -80°C, (5) -150°C, according to the type of biological material. As a general rule, data will be preserved for a minimum term of 10 years. Datasets collected in the context of clinical research, which fall under the scope of the Belgian Law of 7 May 2004, will be archived for 25 years, in agreement with the University Hospital policies and the European Regulation 536/2014 on clinical trials of medicinal products for human use.

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

Physical space in the lab will be provided to store the biological material (refrigerators, cold rooms as well as cupboards for non-degradable materials). Digital data will be stored in the KU Leuven storage space: the KU Leuven L-Drive (virtually unlimited size) has sufficient storage capacity for the outlined project.

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

The annual cost of storage is approximately 569.2 € per 5TB of storage space per year. This cost and capacity include the performance of mirror copies of the stored data, for safety backup purposes. These costs will be covered by the budget of the project leaders.

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:

The key findings of the project and their interpretation will be made available through the publication of journal articles in established, peer-reviewed (non-predatory) academic journals. Relevant raw data will be made publicly available through upload to well-established open-access data repositories.

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

Data may be shared externally upon reasonable requests from collaborating scientists, which will be reviewed and approved on a case-by-case basis by the project leaders. We do not exclude that the proposed work could result in research data with the potential for tech transfer and valorization. The partner institutes have a policy to actively monitor research data for such potential. If there is substantial potential, the invention will be thoroughly assessed, and in a number of cases, the invention will be IP-protected (mostly patent protection or copyright protection). As such the IP protection does not withhold the research data from being made public. In the case a decision is taken to file a patent application it will be planned so that any delay to publication is minimal.

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

We do not exclude that the proposed work could result in research data with the potential for tech transfer and valorization. If there is substantial potential, the invention will be thoroughly assessed, and in a number of cases, the invention will be IP-protected (mostly patent protection or copyright protection). As such the IP protection does not withhold the research data from being made public. In the case a decision is taken to file a patent application it will be planned so that any delay to publication is minimal.

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

Depending on the nature of the dataset both open-access and restricted-access repositories will be used to store data. All requests and approvals for the reuse of data other than those deposited in open-access repositories will be assessed on a case-by-case basis by the project leader.

When will the data be made available?

As study leader, Prof. Massimiliano Mazzone will monitor data-sharing requests. Data will be automatically made available after the publication of results to any requestor using the data for non-commercial purposes. The VIB tech transfer office will negotiate commercial use of the data.

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

Data not deposited in open-access repositories will in principle only be accessible to members of the lab. Other collaborations and sharing are possible with staff and students within the VIB–KU Leuven Center for Cancer Biology and within the KU Leuven Department of Oncology, upon reasonable request. Any user can place reasonable requests for data for non-commercial purposes, and these requests will be assessed on a case-by-case basis by the project leader. Commercial-based requests will be navigated in coordination between the KU Leuven/VIB Tech Transfer team.

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.

- Yes

When relevant PID/DOI/accession numbers will be added to datasets

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

Mainly publication fees. Covered with the FWO budget. Other costs for data sharing will be discussed with collaborators on a case-by-case basis.

6. Responsibilities

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

Data documentation, and metadata acquisition and storage will be performed by the students and postdocs associated with this project. Prof. Massimiliano Mazzone, Marcello Delfini (Staff Scientist) and Dana Liu (Lab Manager) will monitor.

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

Data documentation, and metadata acquisition and storage will be performed by the students and postdocs associated with this project. Prof. Massimiliano Mazzone, Marcello Delfini (Staff Scientist) and Dana Liu (Lab Manager) will monitor.

Who will manage data preservation and sharing?

As study leader, Prof. Massimiliano Mazzone will be responsible for data preservation. He will also monitor data sharing requests. Data will be automatically made available after the publication of results to any requestor using the data for non-commercial purposes. Commercial use of the data will be negotiated through the VIB tech transfer office.

Who will update and implement this DMP?

The lab manager (Dana Liu, lab of Tumor Inflammation and Angiogenesis), staff scientist (Dr. Marcello Delfini, lab of Tumor Inflammation and Angiogenesis) and the PI (Prof. Massimiliano Mazzone) will share the responsibility of updating & implementing this DMP.

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GDPR

GDPR

Have you registered personal data processing activities for this project?

- Not applicable

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DPIA

DPIA

Have you performed a DPIA for the personal data processing activities for this project?

- Not applicable