High-throughput identification of robust collateral sensitivity for antibiotic cycling applications in Staphylococcus aureus wound infections

A Data Management Plan created using DMPonline.be

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Project abstract:

The fast spread of resistance due to the high usage of antibiotics during the last decades has rendered several antimicrobials ineffective and made novel antimicrobial strategies urgently needed. One possible solution is the rational cycling between different antibiotics based on collateral sensitivity, where resistance mutations acquired during treatment with one antibiotic increase susceptibility to a second antibiotic. However, the clinical potential of this strategy has been questioned because the available small-scale experiments do not fully capture the stochastic nature of evolution and do not take into account the in situ treatment conditions. In this research project, we aim to enhance the clinical potential of drug cycling strategies that target Staphylococcus aureus infections in wounds. Hereto, we will identify antibiotics that robustly show a high likelihood of collateral sensitivity (i) by means of a high-throughput screening in which different parameters known to influence resistance development are varied, including population size, bacterial lifestyle and antibiotic gradients and (ii) by screening clinical isolates. Furthermore, the influence of collateral sensitivity on the evolutionary adaptation during drug cycling will be evaluated by combining experimental evolution with an in silico evolutionary model. Finally, the efficacy of drug cycling with the identified antibiotic combinations will be validated in an in vitro and in vivo (porcine) infection model.

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FWO DMP (Flemish Standard DMP)

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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.

				Only for digital data	Only for digital data	Only for digital data	Only for physical data
Dataset Name	Description	New or reused	Digital or Physical	Digital Data Type	Digital Data format	Digital data volume (MB/GB/TB)	Physical volume
		Please choose from the following options: • Generate new data • Reuse existing data	*Please choose from the following options:* • Digital • Physical	*Please choose from the following options:* • Observational • Experimental • Compiled/aggregated data • Simulation data • Software • Other • NA	*Please choose from the following options:* • .por, .xml, .tab, .csv,.pdf, .txt, .rtf, .dwg, .gml, … • NA	*Please choose from the following options:* • <100MB • <1GB • <100GB • <1TB • <5TB • <10TB • <50TB • >50TB • NA	
Biological material	Evolved bacterial strains	Generate new data	Physical	NA	NA	NA	2 mL cryotubes or 96-well plates
Antimicrobial susceptibility tests	Optical density measurements of the MIC and growth rate assays. Cross-resistance and collateral sensitivity networks. Adaptation to the secondary antibiotic and drug cycling *in vitro* and *in vivo*.	Generate new data	Digital	Experimental	.xlsx	<1GB	NA
Time-lapse photography	Images from time-lapse photography of continuous gradient generator	Generate new data	Digital	Experimental	.png	<100GB	NA
Whole-genome sequencing	WGS reads of the evolved bacterial strains	Generate new data	Digital	Experimental	.fastq	<100GB	NA
In silico model	Individual based evolutionary model code	Generate new data	Digital	Simulation data	.py	<100MB	NA
In silico simulations	Simulations with the individual based evolutionary model	Generate new data	Digital	Simulation data	.xlsx	<1GB	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:

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, animal data

WP 4.2 of this project will validate the effectiveness of drug cycling in an *in vivo* guinea pig model, planned from month 42 to 48 in this project. If sufficient *in vitro* data is obtained to support *in vivo* experiments, an application will be filed at the Ethical Committee for Animal Experimentation (ECD) by the start of month 36. Evidently, animal experiments will only commence once the ethical approval is acquired.

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

If this project identifies novel antibiotic pairs that display collateral sensitivity and thus show enhanced killing and a reduced resistance development, these
an inventive benefit based on collateral sensitivity, these combinations can be used to combat wound infections with *Staphylococcus aureus*. Therefore, opportunities to protect intellectual property will be regularly discussed with Leuven Research and Development (LRD), and at least prior to publicly releasing any information.

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).

In the MiCA lab and at the KU Leuven, we work with a sharepoint-based electronic lab notebook. This digital notebook organises all data acquired within a project in a standardized manner and attaches a fixed set of metadata (see below). In addition, separate folders are created for the raw data, processed, and final data.

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

The electronic lab notebook incorporates a fixed set of metadata, including the user coordinating the experiment, the user performing the experiment, the date, and the experimental protocol used

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

Where will the data be stored?

The data will be stored on the hard drive of my laptop, as well as on the SharePoint-based electronic lab notebook (ELN). The ELN is an application hosted on-site within KU Leuven (meaning it is not a cloud storage). Large data files such as microscopy images and whole genome sequencing files will be stored on the internal server of KU Leuven and linked to the ELN. All KU Leuven computers also provide a personal (I) en shared (J) network drive for data storage.

How will the data be backed up?

The ELN and the internal KU Leuven server contains an automatic back-up for the drive capacity that is in use:

- A back-up every few hours (at 9h, 12h30, and 17h), of which the latest 7 versions are saved
- A daily back-up (at 21h), of which the latest 10 versions are saved
- A weekly back-up (Sunday at 11h), of which the latest 6 versions are saved

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

KU Leuven provides easily expandable storage space based on their internal server maintained by the IT service of KU Leuven. Our lab uses two drives on the KU Leuven internal server: the J-drive, and the K-drive. The J-driver is intended for daily use, while the K-drive mainly serves as a long-term storage space.

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

- Access to the ELN only works via KU Leuven Single Sign On
- Each user should have a valid KU Leuven intranet user ID and password
- Permission for access can be defined in detail by the local admin of the SharePoint site
- Biological samples will be stored in a secured -80°C freezer at the facility

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

As the use of ELN is relatively new at KU Leuven, no costs are accounted yet. If costs were to be accounted, they will likely resemble these of

other SharePoint sites with similar storage capacity, which is

- €344.80 for the first year
- €274.80 for the next years

Additional storage space on the KU Leuven internal server can be acquired. Our lab uses two drives on the KU Leuven internal server: the J-drive, and the K-drive:

- The costs for the J-drive are €519/TB/year
- The costs for the K-drive are €100/TB/year

The costs will be covered by the project budget.

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 data will be retained for at ten years according the RDM policy.

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

The KU Leuven internal server via the electronic lab notebook

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

As the use of ELN is relatively new at KU Leuven, no costs are accounted yet. If costs were to be accounted, they will likely resemble these of other SharePoint sites with similar storage capacity, which is

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The costs will be covered by 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.

- Yes, in a restricted access repository (after approval, institutional access only, …)
- Yes, in an Open Access repository

Only published, digital data (antimicrobial susceptibility testing, time-lapse photography, whole-genome sequencing, *in silico* model and simulations) will be made available in an Open Access repository.
Any unpublished data will be made available at the end of the project on KU Leuven's institutional research data repository RDR.

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

Unpublished data on the KU Leuven's institutional research data repository RDR will be restricted to institutional access only.

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.

- No

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

Both published and unpublished data (antimicrobial susceptibility testing, time-lapse photography, whole-genome sequencing, *in silico* model and simulations) will be made available on the institutional research data repository (KU Leuven RDR). A published dataset in KU Leuven RDR gets its own DOI and is automatically reported to Lirias (KU Leuven), FRIS, OpenAire and Google Dataset Search.
Any novel antibiotic resistance genes identified within this project will also be made publicly available on the disciplinary-specific repository "Comprehensive Antibiotic Resistance Database (CARD)".
Published modelling code will be made available on GitHub.

When will the data be made available?

The data will be made available upon publication of research results. Proper links to the datasets will be provided in the corresponding publications.
Unpublished data will be made available on RDR at the end of this project.

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

The shared research data will be protected using a Creative Commons license (CC-BY 4.0).
Modelling code will be protected by a permissive license, such as the MIT license, allowing freedom for re-use, modification and distribution of the software.

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

By sharing published data on the KU Leuven RDR repository, the dataset automatically gets a DOI assigned to it to make them easily citable.

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

KU Leuven staff has free access to the Research Data Repository (RDR), managed by the KU Leuven. For data in alternative repositories, possible costs will be covered by the project budget.

6. Responsibilities

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

Sander Casier

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

Sander Casier and ELN IT Technicians

Who will manage data preservation and sharing?

Sander Casier, ELN IT Technicians and Hans Steenackers

Who will update and implement this DMP?

Sander Casier