STRUCTURE-BASED DESIGN OF INHIBITORS TARGETING THE CHROMATIN-READING FUNCTION OF LEDGF/P75 TO TREAT ACUTE MIXED-LINEAGE LEUKEMIA

A Data Management Plan created using DMPonline.be

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Project abstract:

Mixed-lineage leukemia rearranged (MLL-r) is an acute leukemia mostly affecting children and associated with poor survival. The disease is caused by rearrangements in the MLL gene resulting in malignant fusion proteins. LEDGF/p75 serves as an epigenetic reader and tethers transcription complexes containing MLL to chromatin via its PWWP domain. Recent studies demonstrated that this process is essential for the onset of MLL-r leukemia, yet it is dispensable for hematopoiesis. Consequently, preventing the LEDGF/p75-chromatin interaction should displace the MLL complex from chromatin, downregulate MLL expression and reverse the malignant transformation. Here we propose to design and validate a novel class of small-molecule inhibitors that specifically bind to the nucleosome-recognizing site of LEDGF/p75. First, we will perform a direct crystallographic screening using already obtained PWWP domain crystals and a broad library of drug-like fragments. This recently developed approach is recognized as being efficient and robust. The obtained fragment hits will be grown into potential lead compounds through iterative cycles of in silico design, custom synthesis and biophysical in vitro testing to optimize their affinity and activity. The leads will be further evaluated in cell-based functional assays and eventually using animal models. Our final goal is to create first-in-class lead compounds for acute MLL-r leukemia.

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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)

Protein purification and other biochemical data (lab notes and graphs in digital format)
Collection of custom-synthesized inhibitors (structural formulas and smile strings)
X-ray diffraction data (raw and reflection lists)
Atomic models of protein/ligand complexes (PDB format)
Docking and virtual screens (created by Schrodinger Suite)
In vitro and cell culture data such as inhibition curves (Excel spreadsheets)

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)

1. Steven Beelen (permanent technician/lab manager in Biocrystallography lab) will be responsible for data archivation and storage. This is based on the already existing practice in the lab (for instance, Xray diffraction data have been stored in entirety over the last 10 years).
2. At present, the lab owns a Network Attached Storage (Synology) with 60TB capacity (high-quality 10TB HDDs). We plan to gradually extend this to at least 100TB, depending on demand. The storage is organized as a RAID array. These data files will be preserved for at least 5 years following the completion of the project.

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)

We do not wish to deviate from this principle

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)

No related issues

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

We maintain a collection of all standard experimental protocols in PDF form. There are separate spreadsheets for cloning primers, expression plasmids, etc.

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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.

				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
Proteins	Biochemical data	New data	Digital	Experimental	.pdf	<100GB	
Compounds	Chemical synthesis data	New data	Digital	Experimental	.xls	<1GB	
Diffraction	X-ray data	New data	Digital	Experimental	.img, .mtz	<50TB	
Structures	Atomic coordinates	New data	Digital	Experimental	.pdb	<1GB	
Models	In silico results	New data	Digital	Experimental	various	<1TB	
Activity	In vitro and cell culture data	New data	Digital	Experimental	.pdf	<100GB	

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:

No

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.

- No

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.

- 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.

- 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).

Data sheets per synchrotron session will be kept for all X-ray 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

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

Where will the data be stored?

Lab NAS

How will the data be backed up?

Lab NAS

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

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

The NAS is only for internal use, under a firewall

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

Covered by the FWO funding, several thousand euros

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

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

Lab NAS

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

No extra costs beyond initial storage

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.

- No (closed access)

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

Question not answered.

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, Intellectual Property Rights

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

N/a

When will the data be made available?

N/a

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

N/a

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.

N/a

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

N/a

6. Responsibilities

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

Steven Beelen

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

Steven Beelen

Who will manage data preservation and sharing?

Steven Beelen

Who will update and implement this DMP?

Sergei Strelkov

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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