Biofabrication of remotely actuated skeletal implants using magnetically augmented cartilage-microtissues in alginate microcapsules

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Project abstract:

The multidisciplinary field of Regenerative Medicine has clearly showed its great potential especially with tissue engineered cell based advanced therapeutic medicinal products (ATMPs). Despite being considered as a very promising tool most of the times ATMPs, fail to be translated into clinical practices. There is still a knowledge gap concerning the biomanufacturing and biofabrication processes of these ATMPs, thus limiting their applicability in clinical translation. In this project, we propose an experimental approach following a sequence of processes to develop a high throughput pipeline for the production of osteochondral implants by overcoming limitations faced by traditional biomanufacturing (BMP) and biofabrication strategies. This would be achieved by utilizing a magnetic hydrogel, in which a few hundred of iPS cells would be microencapsulated per microcapsule to form microtissues. Following the proper maturation (bone – cartilage forming populations) and biological evaluation of the microtissues, they will be used to develop through magnetic driven biofabrication, zonated OC implants (bone-cartilage zone) and will be assessed in in vivo transplantation experiments (ectopic) and after magnetic induced mechanical stimulation regimes (knee OC defect). Finally, this novel approach will not be only useful for accelerating research and clinical translation for skeletal ATMPs but it can be adapted as a BMP for any other type of tissue, s.a liver, heart, brain, and skin.

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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)

This project will generate new data using various sophisticated machines and equipment:

1. Microscopes (Olympus, LIMSy, confocal, histological stainings), data will be in .vsi format will be saved in cloud server and their corresponding .jpeg formats are going to be used for presentations and publications; .vsi format includes metadata related to microscope settings. Analyzed data from image analysis would be stored in an excel file and the plots generated with either OriginLab or Graphpad would be also saved in the same file containing the raw data files.
2. MRI, CT scan of in vivo experiments: for this type of data, the rawdata, plus metadata will be stored in the server (L-Driver); all analysis will be stored in the same folder with the analyzed images in a subfolder. Any calculations and analysis on the images will be saved in excel format and it'll be save in the corresponding file location of the sample and experimental protocol used. The processed data would be .jpg images.
3. Videos; with high-speed camera will be saved in .mp4 format and their corresponding analysis with Tracker analysis software would generate tracking results in an excel file format; all of them saved in cloud server in their corresponding sample file location.
4. Magnetic Hysteresis, z-potential measurements; saved in excel file and stored in the cloud server in the location of their corresponding sample and experimental template subfolders. Metadata format is also going to be stored in the same folder.
5. Biophysics analysis; all data used to generate new data in order to analyze the biophysics of our system will be stored in an excel file and their corresponding plots will be visualized in .jpeg images; all of them saved in the cloud server in their corresponding file location described by the experimental template used to generate them.
6. RNA sequencing data; raw and analyzed data will be stored both in the Genomics Core KU Leuven server and in the cloud server of our lab. Analyzed data will be stored in excel files with their corresponding generated plots, while tubes containing a portion of the samples used would be reserved in the lab for at least 5 years after the completion of the research.
7. Material Characterazation: all data obtained using SEM, TEM, FTIR, NMR will be stored in their raw version and the analyzed images and data will be stored in excel and .jpeg formats in the cloud server in the folder corresponding to the project. The samples that were used for this measurements will be also maintained.
8. Publications, draft texts and files used to generate these files will be stored in a seperated folder indicating the publication Journal. Posters, abstracts and presentations in group meetings, conferences and departmental meetings will be also saved in a separeted file in the cloud server. The format of these data will vary from .word files to PDF and ppt presentantions.
9. Any data generated from computational models will be saved in their raw file version and proccessed data will be found in the same folders with the rawdata they describe.

We expect that by the end of the funded fellowship the project will generate new data with **an estimated volume around 3-3.5TB.** The cloud server of our lab will facilitate the data storage for up to 5 years after the completion of this project and special SSD external hard drivers have already been purchused for storing nanoCT and MRI data that have the biggest volume; the hard drivers will be maintained as lab's property and we will guarantee their availability for up to 5 years after the completion of the project; the data stored in SSD hard drivers will also be stored in the cloud server as a backup; but for their analysis the hard drivers must be used (faster analysis).

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)

Designation of responsible person:

PI: Ioannis Papantoniou and Lab Manager: Jenny Peeters

Storage capacity/repository

- during the research: will be stored in Cranium (L driver), Total Capacity: 8 PetaBytes= 8.000.000 GB for all users of the lab.
- after the research: important data will be maintained in Cranium for up to 5 years after the completion of the research, since the research included human derived specimens it is important that some of the data will have to be saved and reported to the ethical committe upon request. For this type of data we will guarantee their availability even longer after the expire of the 5 year period.

Therefore we believe that we will not meet any problems regarding the storage of these data. Moreover, since we are using human cells in this research, we have to report their usage to ethical commite upon request and maintain the original files.

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)

N/A

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)

In this project we do not have, store or use any personal data of human participants/donors. Data derived from the use of human biological material would be stored and maintained for reporting back to the ethical committe upon request even after the end of this project.

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

At the moment, we do not have any issues or limitations regarding data management

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DPIA

DPIA

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

- No

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GDPR

GDPR

Have you registered personal data processing activities for this project?

- No

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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
		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, .cvs,.pdf, .txt, .rtf, .dwg, .gml, … • NA	*Please choose from the following options:* • <100MB • <1GB • <100GB • <1TB • <5TB • <10TB • <50TB • >50TB • NA	
Material characterazation	Material analysis on hydrogel and tissue	Generate new data	Digital Physical	Experimental observational	.tif, .jpg, .ppt, .pdf, graphs	50GB	Materials analyzed kept for reference
Microscope analysis	Mic images from biological samples	generate new data	Digital Physical	Experimental observational	.jpg, .ppt, .tif, data: .excel, graphs	1TB	Slide boxes with sections kept in the lab
MRI-nanoCT scan	in vivo imaging	generate new data	Digital	Experimental	raw data, .jpg, .pdf	1-2 TB	
H-speed Videos	video	new data	DIgital	Observational	.mp4, .tif, tracker software format, .excel	100GB	
RNA-seq	mRNA expression	New data	Digital	Experimental/aggregated data	.excel file	1-1.5TB	
Poster-Publications	-	Reuse existing data			.ppt, .pdf	100GB	
Biophysics	observations and simulations	new data	Digital	Experimental, Observational + Simulation Data	.mp4, data from comsol	150GB	

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

In this project we do not have, store or use any personal data of human participants/donors .
Data derived from the use of human biological material would be stored and maintained for reporting back to the ethical committe upon request even after the end of this project.
The biological samples derived from humans have been approved by ethical commite and the codes for their experimental use are:
For the EC human periosteum derived cells: it is S53717 and S64471 **For the EC iPS cells:** it is S66219 Since for this research we planned in vivo implantations in animals: **For the EC animalium** it is P059-2020 **mouse ectopic and orthotopic model For the EC animalium** it is P056-2019 **rat knee joint model**

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

In this project we do not have, store or use any personal data of human participants/donors .

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

In this research they are 2 components that can have great valorization value.
1st valorazation opportunity is the encapsulation technik and material after the end of WP2. Although as a technik isnt new and its widely used in state of the art companies to encapsulate biological material (TreeFrog) in order to bioprocess them and cultivate them, the use of magnetic nanoparticles and thus the magnetic actuation of the droplets with the encapsulated stem cells opens new possibilities in the way that these samples are treated during the downstreaming processes. Thus, we believe that it would be viable for commercial exploitation.
2nd valorazation opportunity is the magnetic driven assembly of microtissues into bigger biological samples as well as their biological behaviour upon culture under magnetic field WP3-4. We are currently conducting experiments to evaluate if this process step of bioassembly offers further enhancement for the phenotype of the implants that we aim to produce.
A Non-invesively visualization of implants with MRI would also let us explore any possibilities for clinical translation options.
After gathering the data and producing ppt presentations and pdfs we will consult with the LRD department. Main goal is the establishment of a spin-off/start up company within KU Leuven for further exploitation of this research.

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

NA

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).

Experimental templates describing analytical the experimental procedure as well as the instruments usage and settings will accompany the folder where the raw data will be stored, giving the future user the ability to understand, retrieve infromation and recapitulate the research.

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.

- Yes

Metadata file from highly speciallized instruments will be stored and maintained

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

Where will the data be stored?

In Cranium, L Driver provided by KU Leuven: 8 PetaBytes volume capacity.
Backup files stored in SSD hard drivers to make analysis easier and faster.

How will the data be backed up?

NA

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

There is enough storage capacity in L drive to save the estimated output of our research (2TB)

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

Data are stored in L Driver, thus users affilieted strictly with KU Leuven and in particular our Lab will only have access; every user having access to the L driver signs a doc related to the crecedential rights of use;

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

NA

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...).

Data obtained by using human derived biological material will be maintained and used for reporting to ethical committes. Data will be stored for 10 years.

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

In L driver, KU Leuven storage solution

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

NA

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, …)

All data generated will and could be used for access within our group.
In case of spin-offs the data will be stored in a restricted access repository.

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

PI - Ioannis Papantoniou
Researcher: Konstantinos Ioannidis

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

Technological aspects of the projects will be the intellectual property of this Project.
In case of publications, the datasets and rawdata would be available for sharing via the Journal.

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

In L Driver, they are stored, saved and available as soon as they are getting generated

When will the data be made available?

Upon Generation for raw data, and upon publication of research results of the analyzed processed version of data.

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

NA

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.

- No

NA

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

NA

6. Responsibilities

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

Konstantinos Ioannidids, Ioannis Papantoniou

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

Konstantinos Ioannidis

Who will manage data preservation and sharing?

Ioannis Papantoniou

Who will update and implement this DMP?

Ioannis Papantoniou