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JOB OFFER – *Post-Doc*

A postdoctoral research position is available to participate in a research that has been designed to study the role of the liver- and HSPCs-derived ComC in homing, engraftment, and post-transplant expansion of Hematopoietic Stem Progenitor Cells

Project Title:

"The novel view on circulating and hematopoietic stem cell-expressed complement in hematopoietic posttransplant recovery"

Project Background:

Hematopoietic transplantation is performed by intravenous infusion of donor-derived or autologous hematopoietic stem progenitor cells (**HSPCs**), which, in response to bone marrow (**BM**)-expressed chemoattractant navigate and home to BM hematopoietic niches. This process is followed by their engraftment and expansion to repopulate the recipient's BM myeloablated before transplantation. The most important BM chemoattractant is the α-chemokine stromal-derived factor 1 (SDF-1). However, its homing role is supported by the bioactive phosphosphingolipid sphingosine-1-phosphate (S1P) and by extracellular adenosine triphosphate (eATP). As we demonstrated in the past, the CXCR4 receptor for SDF-1 must be incorporated into cell surface membrane lipid rafts (**MLRs**) for optimal SDF-1 gradient sensing by HSPCs. Our previous research demonstrated that an important and for many years underestimated role in hematopoiesis plays an innate immunity soluble arm that is complement cascade (**ComC**). We provided evidence that ComC becomes activated in BM during pharmacological mobilization in response to granulocyte colony-stimulating factor (G-CSF) or CXCR4 receptor antagonist AMD3100. In this proposal, we will focus on the role of ComC in a reverse phenomenon that is the posttransplant homing/engraftment of HSPCs. It is known that the critical step before infusion of HSPCs is the myeloablative treatment of the recipient aimed to destroy pathological hematopoiesis and empty BM niches to provide space available for new transplanted HSPCs. Myeloablative treatment involves high-dose chemotherapy or myeloablative irradiation. In experimental animal transplant models, lethal irradiation is a standard procedure. The available literature indicates that both irradiation and chemotherapy induce in various organs and tissues similarly as during mobilization, a state of sterile inflammation and extracellular ATP (eATP) released from damaged cells triggers this process. We postulate that the same occurs in the BM microenvironment, and in fact, our preliminary data shows that **ComC** becomes activated in mice after

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myeloablative conditioning for transplantation by lethal γ-irradiation or exposure to myeloablative chemotherapy. It is known that ComC could be activated by *i)* classical-, ii) mannan-binding lectin, or *iii)* alternative-pathway.

Activation of ComC leads to the release of C3 and C5 complement components cleavage fragments - C3a and C5a anaphylatoxins that are processed by serum carboxypeptidase to $_{desArg}$C3a and $_{desArg}$C5a as well as leads to the formation of C5b-C9 or non-lytic or lytic membrane attack complex (MAC), which is the terminal product of ComC activation. On the other hand, both HSPCs and cells in BM microenvironment express receptors for C3a and C5a (C3aR, C5aR1, and C5aR2). After myeloablative therapy, active ComC cleavage fragments circulate in PB. Therefore, HSPCs infused into the transplant recipient's bloodstream are exposed to these potent innate immunity mediators. This interaction of HSPCs with ComC meditators, as we propose, promotes better navigation of infused cells to the recipient BM niches, and we hypothesize it is a result of the promotion of MLRs formation on HSPCs. On the other hand, myeloablative conditioning for transplantation induces a state of sterile inflammation in transplant recipient BM to facilitate homing and engraftment of circulating in PB transplanted HSPCs. Finally, new intriguing evidence accumulated that, in addition to the liver ComC synthesis also occurs inside some cells – e.g., in lymphocytes. Our recent data indicate that the same phenomenon occurs in HSPCs. Therefore, the intercellular expression of ComC elements known as **complosome** sheds a new light on the underappreciated role of innate immunity in regulating hematopoiesis. Based on this, to study the role of liver- and HSPCs-derived ComC in homing, engraftment, and post-transplant expansion of HSPCs, and design optimal hematopoietic transplantation protocols, we propose three interrelated aims.

Specific Aim 1*. To learn which of the ComC activation pathways (classical, mannan-binding lectin, and/or alternative) is crucial in response to radio- chemotherapy-mediated myeloablative conditioning for transplantation to promote homing and engraftment of HSPCs?*

Specific Aim 2. *Effect of ComC cleavage fragments on infused HSPCs "navigating" to recipient BM. We will focus on the role of ComC cleavage fragments in promoting responsiveness of HSPCs to BM homing factors, after infusion into PB of a transplant recipient.*

Specific Aim 3. ***Specific Aim 3****. To identify ComC activated events in BM microenvironment of myeloablated for transplantation recipient that facilitate homing, engraftment, and subsequent expansion of HSPCs, and to shed more light on the significance of endogenous expression of ComC proteins in HSPCs (complosome) - that as we hypothesize supports engraftment and expansion of transplanted HSPCs in BM.*

We are looking for a highly motivated person to participate as a post-doctoral fellow within scientific project at the Warsaw Medical University at the Department of Regenerative Medicine

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Supervisors: Mariusz Ratajczak, MD, PhD,
Type of employment relationship: Contact of mandate
Employing entity: Warsaw Medical University
Application deadline: November 30st, 2023
Expected start date: January 2024
Duration: 26-month position
The position is offered for a maximum period of 26 months with an initial probation period of 6 months.
Salary: 11 600 PLN (**tax included)- (gross plus employers fees**)

Eligibility:
A suitable applicant should have the following qualifications:

1. PhD degree in Biology or Biotechnology
2. Basic previous experience in the following biology techniques: RNA seq, Mass Spectrometry, flow cytometry, imaging
3. Academic background in cell biology, molecular biology, and/or genetics.
4. Scientific research experience (full-text international publications, full-text articles published in Polish journals, international abstracts, active participation in (inter)national meetings, and scientific courses)
5. Ability to work independently
6. The candidate is required to have knowledge of stem cell biology
7. Good knowledge of English
8. Strong interest in science

How to apply:
Please send:

1. Letter of interest
2. CV
3. Publication list
4. Photo
5. Contact details of 1-2 potential referees with **recommendation letter**

to:
mariusz.ratajczak@wum.edu.pl
medycyna.regeneracyjna@wum.edu.pl

All documents should be sent as PDF files.

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The e-mail heading should be: „**Post-doc – OPUS grant”.**

Please provide also the statement that you grant us a permission to process your personal details for the recruitment process:
“I hereby give consent for my personal data included in the job offer to be processed for the purposes of recruitment conducted by the Medical University of Warsaw located in Warsaw”.

The rules for the protection of personal data used by the Medical University of Warsaw:

1. The administrator of personal data is the Medical University of Warsaw located in Warsaw, Żwirki i Wigury 61, 02-091 Warszawa,
2. Contact to the Data Protection Officer - email address: iod@wum.edu.pl.
3. Personal data will be processed in order to implement the recruitment process pursuant to art. 22^1 of the Labor Code, and in the case of providing a broader scope of data pursuant to art. 6 § 1a GDPR - consent expressed by the candidate.
4. Access to personal data within the University's organizational structure shall only have employees authorized by the Administrator in the necessary scope.
5. Personal data will not be disclosed to other entities, except for entities authorized by law.
6. Personal data will be stored for the period necessary to carry out the recruitment process, up to 12 months from the settlement of the recruitment process. After this period, they will be removed.
7. You have the right to access your data, the right to rectify, delete, limit processing, the right to transfer data, the right to object to the processing, the right to withdraw consent.
8. You have the right to withdraw consent to the processing of your personal data at any time, which will not affect the lawfulness of the processing that was carried out on the basis of consent before its withdrawal.
9. You have the right to lodge a complaint with the Office for Personal Data Protection when it is justified that his personal data are processed by the Administrator in breach of the general regulation on the protection of personal data of April 27, 2016.
10. Providing personal data is voluntary, but necessary to participate in the recruitment process to the extent specified in art. 22^1 § 1 of the Labor Code, voluntary in the remaining scope.
11. Decisions will not be taken in an automated manner and personal data will not be subject to profiling.

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