PUBLIC NOTICE OF OPENING OF AN INTERNATIONAL RECRUITMENT COMPETITION FOR ONE PHD HOLDER FOR THE PROJECT "BONE-PURI(NO)AGEING - REGENERATION OF THE AGEING HUMAN BONE BY PURINOME-ACTIVATED MESENCHYMAL STEM CELLS – PRE-CLINICAL STUDIES", AT ICBAS-UP (FIXED-TERM CONTRACT)

1. The Dean of the Institute of Biomedical Sciences of Abel Salazar of the University of Porto (ICBAS-UP) approved on June 18, 2021, the opening of an international recruitment competition for a PhD holder to carry out research in the area of Basic Medicine, by means of an individual fixed-term employment contract ("contrato individual de termo resolutivo incerto") under the Portuguese Labour Code. The successful candidate will work in the research project "BONE-PURI(NO)AGEING – Regeneration of the ageing human bone by purinome-activated mesenchymal stem cells – pre-clinical studies", with the reference POCI-01-0145-FEDER-029398, supported by COMPETE 2020, Portugal 2020 and the European Union through the ERDF, and by FCT through national funds
The researcher will join a project intended to search for new strategies to recover the original cell phenotype of aged bone marrow-osteoprogenitor mesenchymal stem cells from postmenopausal (PM) female patients, for future cell-based therapies.

Within this context, it is well accepted by the scientific community that senescence of bone marrow mesenchymal stem cell (MSC) osteoprogenitors is one possible explanation for the high prevalence of osteoporosis among aged people, which also limits their use in bone tissue repair. Nucleotides, such as ATP, are released to bone microenvironment under physiological mechanical stimulation, but their levels increase dramatically by bone injury. Once released, they bind to multiple P2 purinoceptors (P2Y and P2X) on osteoblasts and osteoclasts modulating bone remodelling. Their action can be rapidly terminated by a cascade of membrane-bound ecto-NTPDases. Indeed, several studies correlated age-induced loss of ability of MSCs to differentiate into bone forming cells, osteoblasts, to changes in the amount of adenine and uracil nucleotides accumulated in bone microenvironment. Our findings demonstrate that osteogenic differentiation of MSCs is impaired in PM women vs. younger females and we have identified two purinoceptors (P2X7 and P2Y6) as being most important promoters of osteogenic differentiation of MSCs. In PM women, the lack of activation of P2X7 and P2Y6 receptors and, thus, the osteogenic potential of MSCs is severely compromised by overexpression of NTPDase3. These findings prompted us to hypothesize that the "purinome", comprising nucleotide release sites, NTPDases and purinoceptors, could be a novel

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target to re-habilitate the osteogenic potential of aged MSCs. Bypassing age-related constrains of MSCs would be much appreciated, allowing their use in bone repair techniques (e.g. autologous bone engrafting) for rapid physical recovery of bone defects in aged (osteoporotic) patients. To avoid collateral damages and rejection of heterologous bone grafts, our approach predicts the use of purinome-activated autologous MSCs expanded in vitro and re-injected into bone defects by a minimal invasive surgical technique. Rehabilitation of aged MSCs will be done during clonal expansion in conditioned media containing specific P2X7 and/or P2Y6 receptor activators. Alternatively, accumulation of endogenous nucleotides in bone microenvironment is favoured (1) by growing the cells under controlled mechanical strain, and/or (2) by silencing the nucleotide inactivating NTPDase3 gene expression and activity with specific interference RNAs (shRNA), enzymatic drug inhibitors and blocking antibodies (e.g. hN3-B3S). Due to ethical constrains, preclinical tests of bone regeneration using purinome-activated human MSCs will be carried out in a bone critical defect rat model.

The purpose of this contract is to perform the following tasks:

a) To isolate, expand and phenotypically characterize bone marrow MSCs from young women and PM female patients in osteogenic medium in the presence/absence of specific purinoceptor agonists/antagonists and with NTPDase3 inhibitors (chemical inhibitors, selective antibodies and RNAi);
b) Implement a drug-free mechanical cell stimulation method, capable of restoring the original osteogenic phenotype of MSCs of PM women by favoring the accumulation of nucleotides in the bone microenvironment; for this, the cells will be cultured under mechanical agitation using a MechanoCulture FX system and the accumulated ATP will be measured by bioluminescence;
c) To characterize morphologically, enzymatically, biochemically and functionally the MSCs in culture using several molecular markers of osteogenic differentiation, Ca2 + signals in single cells and immunofluorescence applied to confocal microscopy;
d) Establish routines for the generation and characterization of bone critical defects in rats in order to conduct pre-clinical trials to assess bone regeneration using activated human MSCs, which after in vitro clonal expansion (points 1-3) and conjugation with collagen microspheres (PLGA / ColI), will be implanted by minimally invasive procedures.
e) To evaluate bone mass by in vivo fluorescent imaging (ChemiDoc) using the hydroxyapatite Xenolight Rediject Bone Probe 680; in addition, cortical and trabecular bone density (femur) will be evaluated using high-resolution micro-computed tomography (microCT) and by histological examination post mortem.

This project is aligned with MEDINUP fundamental goals, namely the Molecular Target and Cell Signaling Group, which predicts the existence of a narrow collaboration between basic and clinical sciences on the discovery of new targets with plausible therapeutical impact. This project also involves Othopedic Surgeons from the Centro Hospitalar de VN de Gaia-Espinho (CHVNG, hospital) and the Centro Hospitalar Universitário do Porto (CHUP), and the University of Laval, Canada. All procedures were previously validated by the ethic committees from CHVNG, CHUP and ICBAS-UP. For further information, please refer to the following references:

1) Noronha-Matos JB and Correia-de-Sá P, 2016. Journal of Cellular Physiology 231, 1852-1861.
2) Noronha-Matos JB et al., 2014. FASEB Journal 28, 5208-5222.
3) Burnstock G et al., 2013. Purinergic Signalling 9, 541-572
4) Noronha-Matos JB et al., 2012. Journal of Cellular Physiology 227, 2694-2709
5) Raggi C and Berardi AC, 2012. Muscles, Ligaments and Tendons Journal 2, 239-242
6) Costa MA et al., 2011. Journal of Cellular Physiology 226, 1353-1366.

Termination of the project or termination of the financing shall determine the expiration of the contract.

2. Applicable law

Decree-Law No. 57/2016, of August 29, the regulations for hiring PhD holders to stimulate scientific and technological employment in all areas of knowledge (RJEC), with the amendments introduced by Law No. 57/2017, dated July 19, also taking into account the provisions of Regulatory Decree No. 11-A/2017, of December 29; Regulamento do pessoal de investigação, de ciência e tecnologia da Universidade do Porto – Regulamento n.º 487/2020;Portuguese Labour Code, approved by Law No. 7/2009, of February 12, in its current wording.

3. Under the terms of Article 18 of RJEC, the present competition is exempt of: i) authorization from the Government officials in charge of the areas of Finance and Public Administration, as specified in point 3 of Article 7 of the Public Service Labour Law ("Lei de Trabalho em Funções Públicas – LTFP"); ii) prior favourable opinion from the Government officials in charge of the areas of Finance and Public Administration (as specified in point 5 of Article 30 of the LTFP); and iii) the legal procedure for the recruitment of workers in the process of requalification, as specified in Article 265 of the LTFP.

4. In compliance with Article 13 of RJEC and Article 22.º of Regulamento n.º 487/2020, the selection panel of this competition is composed as follows:

Chair:
Paulo Correia de Sá, MD, PhD, Full Professor from ICBAS-UP;
Jury Members:
José Bernardo Noronha-Matos, Biochem, PhD, Assistant Professor from ICBAS-UP
Maria Adelina Costa, PharmD, PhD, Assistant Professor from ICBAS-UP
Alternate members:
Fátima Ferreirinha, Biol, PhD, Scientific Advisor from ICBAS-UP
Graça Lobo, PharmD, PhD, Assistant Professor from ICBAS-UP

5. The work will be developed at Laboratório de Farmacologia e Neurobiologia, MEDINUP - Centro de Investigação Farmacológica e Inovação Medicamentosa (Grupo de Alvos Moleculares e Sinalização Celular), Instituto de Ciências Biomédicas de Abel Salazar (ICBAS), University of Porto, Rua Jorge Viterbo Ferreira 228, 4050-313 Porto.

6. The monthly remuneration to be paid is of €2.134,73, corresponding to level 33 of the Single Salary Table, approved by Order no. 1553-C/2008 of December 31 and level 5, position 1 from the Regulamento n. º 487/2020.

7. The competition is open to national candidates, foreigners and stateless persons who hold a doctoral degree in Biomedical Sciences, Medicine, Veterinary Medicine, Pharmaceutical Sciences, Biochemistry, Biology or related areas and a scientific and professional path that reveals an adequate profile to the activity to be developed.

If the candidate holds a doctoral degree awarded by a foreign higher education institution, it must be recognized by a Portuguese higher education institution, in accordance with the provisions of article 25 of Decree-Law no. 66/2018 of 16 August, which approves the legal regime for the recognition of academic degrees and higher education diplomas awarded by foreign higher education institutions and Article 4 (2) (e) of Decree-Law no. 60/2018 of 3 August, and any formalities established therein be fulfilled up to the date of the contracting act.

8. According to Article 5 of RJEC, the selection is made through the evaluation of the scientific and curricular path of the candidates.

9. The evaluation of the scientific and curricular path of the candidates focuses on the relevance, quality and timeliness of:

a) The scientific–production of the last five years considered to be more relevant by the applicant;
b) The applied or practice-based research activities developed over the last five years and considered as having the greatest impact by the candidate;
c) The activities of extension and dissemination of knowledge developed during the last five years, considered to be of greater relevance by the candidate.

10. The period of five years referred to in the previous number may be increased by the selection panel, at the request of the candidate, when justified in suspending the scientific activity for socially protected reasons, namely for reasons of parental leave, serious illness prolonged work, and other situations of unavailability for work legally protected.

11. Special requirements for admission:
a) Proven professional experience in methods of detecting and measuring substances in biological tissues and liquids (e.g. high-performance liquid chromatography (HPLC), mass spectrometry, capillary electrophoresis and/or bioluminescence);
b) Professional experience in cell culture techniques, immunohistochemistry and confocal microscopy, including the use of fluorescent probes to measure intracellular Ca2 +;
c) Professional experience in molecular biology techniques (Western-blot and / or RT-PCR, RNAi);
d) Have at least 4 scientific publications in international journals indexed in the InCites Journal Citation Reports on topics related to the experience required in the project, namely within the scope of cellular and molecular biology techniques, preferentially involving purinergic signaling.

12. Preference will be given to candidates who have the following experience proven through the authorship / co-authorship of scientific articles published in peer-reviewed international journals:
a) Accreditation as a competent person to practice animal experimentation (Laboratory Animal Science course, categories B or C from FELASA);
b) At least 5 years of proven scientific experience in the scope of the mechanisms involved in purinergic signaling;
c) At least 5 years of experience in the measurement of purine content by HPLC, mass spectrometry, capillary electrophoresis and/or bioluminescence;
d) At least 5 years of experience in immunofluorescence techniques applied to confocal microscopy and in the use of fluorescent dyes for intracellular calcium measurements;

e) At least 5 years of experience on tissue isolation and subsequent cell culturing procedures.
f) Authorship or participation in national/international patent applications.

13. Evaluation methods are: scientific and curricular path:

a) The candidates will be ranked on a scale between 0 - 100 points, based on their curriculum vitae (AC), scientific profile (PC) and motivation letter (CM).
b) Evaluation criteria will use the following formula: quality of the curriculum vitae (AC, 0 - 30 points); adequacy of the candidate's profile that meet project needs (PC, 0 - 60 points) and motivation letter (CM, 0 - 10 points), on a scale between 0 - 100 points.
c) The quality of the candidate's curriculum vitae (AC) will focus on the relevance, quality and novelty of presented details: academic graduation, master and doctoral grades (0 - 10 points); scientific production considered of greater impact by the candidate (authorship/co-authorship of scientific papers in indexed journals, oral or panel communications in congresses, awards, patents, among others) (0 - 15 points); and dissemination of knowledge and extension of activities considered of greater impact by the candidate (0 - 5 points), on a scale of 0 - 30 points.

If necessary, the Interview (E) will be conducted to the three best placed candidates after the curriculum evaluation, and is intended to clarify aspects related to their research and science communication and awareness, weighing 10 % for final rating. The jury may waive the interview if the number of candidates who meet the special requirements for admission to the competition is equal or less than two.

14. The final score (FS) to each of the candidates is expressed on a scale of 0 to 100 points.
FS = AC + PC + CM
FS with interview = (AC + PC + CM) * 0.90 + E * 0.10

15. The selection panel will make decisions based on the selection criteria above using nominal voting (voting by roll call). Abstentions are not allowed.

16. Minutes of the selection panel meetings will be drawn up containing a summary of what has taken place in them, including the votes cast by each of the members and respective justification. Minutes will be available to the applicants if requested.

17. When the selection procedure has been concluded, the selection panel will elaborate a sorted list of successful candidates based on the obtained scores.

18. The final decision of the jury is approved by the maximum leader of the institution that also decides on the hiring.

19. Submission of applications:

19.1. Candidates must submit their applications, addressed to the Chair of the selection panel, identifying the competition they are applying to, full name, affiliation, number and date of issue of identification card, citizen's card, or passport, tax identification number, date and place of birth, home and contact address, including e-mail address and telephone number.

19.2. Applications must include all supporting documents that prove that the conditions set out in the requirements (points 7 to 12) are fulfilled, in particular:

a) Copy of PhD certificate or diploma;
b) Prove of demanded experience, namely recommendation letters or candidate's published scientific papers;
c) Detailed Curriculum Vitae including a brief description of the most relevant scientific and university extension activities of the last 5 years according to paragraph 2 of article 5 RJEC;
d) Motivation letter;
e) Other supporting documents that the applicant considers relevant for the assessment of its merit.

19.3. Applicants submit their requirements and supporting documents in PDF format to the electronic address candidaturasrh@sp.up.pt, and also to farmacol@icbas.up.pt. In the subject of the message, please include the reference of the post "ICBAS | 1 Investigador/a Doutorado/a | BONE-PURI(NO)AGEING"

19.4. Applications must be submitted by 11.59 pm (local time) on the 10th working day following the publication of this notice in the 2nd series of the Diário da República, on the Bolsa de Emprego Público, on the Euraxess portal, on the University of Porto's Recruitment page and ICBAS website).

20. Candidates whose applications are not properly completed or who fail to fulfil the requirements established in the call are excluded from admission. In case of doubt, the selection panel is entitled to request further documentation to support the applicant's declarations.

21. False statements provided by applicants are punishable by law.

22. The minutes regarding the evaluation phases will be sent by email to the address provided by the candidates on their Curriculum Vitae.

23. Prior hearing and deadline for final decision: in compliance with the provisions of the Article 121 of the Code of Administrative Procedure ("Código do Procedimento Administrativo"), after being notified, candidates have 10 working days to submit a formal rebuttal. p to a maximum of 90 days counted from the deadline for submitting applications, the selection panel will have passed the final decisions.

24. This selection is exclusively intended to fill this available position. It may be closed at any time before the legally binding homologation of the final ranking lists, and will expire when the position is filled.

25. ICBAS-UP actively promotes a policy of non-discrimination and equal access, so that no candidate can be privileged, benefited, disadvantaged or deprived of any right or exemption from any duty owing, in particular, to ancestry, age, sex, sexual orientation, marital status, family status, economic situation, education, social origin or condition, genetic heritage, reduced working capacity, disability, chronic illness, nationality, ethnic origin or race, territory of origin, language, religion, political or ideological beliefs and trade union membership.

26. The selection panel approved this public notice at the meeting held on May 24, 2021.

Porto, 18 June, 2021

The Dean of the Institute of Biomedical Sciences of Abel Salazar of the University of Porto, Professor Doutor Henrique Cyrne Carvalho