Report of scientific, translational, innovation and societal events - 2020

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Yearly report of activities – 2020

A changing environment to build MIA-Portugal:

As is common knowledge but is still critical to be kept in mind beforehand, all activities during this year were severely conditioned by the successive lockdowns and limitations imposed by the emergence and re-emergence of COVID pandemic. This is most especially true for biomedical activities since several professionals were forced to re-allocate their priorities and time schedules to an unforeseen support required to cope with this new reality. This was particularly evident for some key scientific staff supporting the implementation of MIA-Portugal, who devoted a considerable time to the implementation of laboratory support to the detection of Sars-Cov2, as best heralded by the recognition of the Laboratory of Microbiology of the Faculty of Medicine (led by the MIA-Portugal support researcher Teresa Gonçalves) as one of the national reference units in the diagnosis of Sars-Cov2. Additionally, the University rightly chose as a priority to implement an analysis unit that still guarantees the screening of the majority of the population in the central area of Portugal. This effort implied a profound re-organization of laboratory facilities, of research staff working on a volunteering basis and of the engineering units of the University to the build-up of these facilities, as a concerted priority effort of critical social need to face this unexpected health crisis. Unsurprisingly, there was a limitation in the availability of attention and of means to develop all other activities within the University.

Despite these severe constraints imposed by this crisis situation, the MIA-Portugal project remained a priority within the University of Coimbra, as testified by the effort to meet all the goals planned for this first year of project execution, albeit there was a need to downsize the anticipated amplitude of some of the activities. As detailed in this report, several of these aims that were downsized in amplitude were not necessarily established as contracted milestones, but were nevertheless important co-adjuvants for the blossoming of the project.

1-Implementation of the managing structure of MIA-Portugal:

The major efforts made this year were directed to the implementation of the managing structure of MIA-Portugal. The establishment of the bylaws of MIA-Portugal and of some of its ruling bodies demanded a tight and productive interaction with several bodies of the University of Coimbra, which not only allowed reaching optimized solutions but also triggered fruitful discussions with different executive bodies of the University of Coimbra that questioned some of their procedures and raised awareness for the need to alter some other operating rules. The process of organizations of the bylaws of MIA-Portugal was made particularly easier thanks to the engagement in their preparation of the vice Dean for Research of the University of Coimbra, Claúdia Cavadas, who is also a support researcher of MIA-Portugal's project.

Always under the guidance of Claúdia Cavadas to ensure an optimal articulation of MIA-Portugal with the University, we proceeded to implement the Ethics Advisory Board, the International Advisory Board, the Advocacy Committee and the Installation Committee, all approved by the Dean of the University of Coimbra. Installation Committee members were

kept informed of the evolution of the installation of MIA-Portugal with a formal meeting (now forcefully digital) every six months. An informal executive committee led by Claudia Cavadas and the Scientific Manager of the project (Rodrigo Cunha) handle all daily problems, and regularly contacts the executive representatives of Newcastle (Thomas von Zglinicki) and Groningen (Faulkert Kuipers) to seek for any required advise. In order to discipline these contacts and ensure regular update of advances in the project, it was recently decided to do a monthly digital meeting.

Additionally, the financial and project managing of MIA-Portugal is ensured by a team led by Alexandre Leal with Filipa Ferraz and Sónia Abrantes as Financial Officer. This administrative unit imbedded within the University of Coimbra and working side-by-side with the services of the University has been paramount to ensure a smooth implementation of MIA-Portugal, while presenting a dynamic that contributes to bolster the overall efficiency of the University's services. Indeed, the implementation of this managing structure within the University of Coimbra also fulfilled another major goal of MIA-Portugal, i.e. to positively influence the excellence of processes within the University of Coimbra. Thus, the dynamics implemented in the managing structure of MIA-Portugal has also been a leitmotif for optimization of the functioning of units within the University dealing with project managing and acquisition processes. Although these features might seem a minor outreach goal, they are undoubtfully a major positive twist to amelioration of the support provided by the University in general, which fully justify the option to develop MIA-Portugal within the realm of the University of Coimbra.

2-<u>Recruitment of the first PIs of MIA-Portugal</u>:

As a research-based structure, a keystone process to formally launch activities intrinsic to MIA-Portugal is the recruitment of the principal investigators (PIs). According to the scheduling of activities of the project, we launch the process of recruitment of the first two PIs of MIA-Portugal during this first year. We implemented a two steps process for these recruitments. First, we launched in February a call for expression of interest. This was of critical importance to understand how we could profile the official announcement to maximize the inclusion of the candidates with the profile we were looking for while making it evident for candidates with profiles not fitting our scope, that they should not consider applying. Although this process seems aberrant, it was of uppermost importance so that the preferences of the jury might not be overruled by legal constraints imposed by the rigid rules of hiring for public positions in Portugal. The jury evaluating the applications was composed by a representative of the Dean (C.Cavadas, vice-Dean for Research at the University of Coimbra), the current scientific coordinator of MIA-Portugal (RA Cunha), the president of the largest and most prestigious biomedical research center at the University of Coimbra (J Ramalho, president of the Center for Neuroscience and Cell Biology) and two representatives of our partners at MIA-Portugal, T. von Zglinicki (Newcastle Univeristy) and F. Kuipers (University Medical Center Groningen). The jury made a pre-selection of the five more promising candidates, among 35 candidates, who were individually interview via Zoom, to allow the selection of two truly outstanding candidates, Nuno Raimundo and Ira Milosevic, researchers from Gottingen and Oxford. Both have already confirmed acceptance of the positions and we have delayed theeofficial beginning of their contracts simply because of the current difficulties to move in Europe.

Apart from fulfilling this primary goal of selecting remarkable candidates, this process of selection also had an impact on the hiring procedures operating at the University of Coimbra. In fact, this procedure was paramount to increase awareness for the need to find creative solutions within the existing legal constraints to increase the speed and the flexibility of these selection processes, with the efforts and commitment of the personal involved.

3-Instalation of the new PIs and new facilities of MIA-Portugal:

The installation of MIA-Portugal within the University of Coimbra represents a major opportunity for the development of biomedical research within the University, namely through the construction of a new research building to host MIA-Portugal together with several support groups of excellence already working at the University of Coimbra.

Major steps were achieved this year towards making this new building a reality within the near future. First, we completed the process of classifying this endeavor as a priority within the roadmap of scientific institutions by the Portuguese government, a condition *sina qua non* for the project to become officially authorized. In parallel, the plans of the building were completed and negotiations with the city's hall were completed to approve the construction of the building in the grounds of the University near the Hospital and the Faculties of Medicine and Pharmacy. Lastly, the Portuguese Science Foundation approved the plans of building this new research facility, which was a mandatory condition to use funds from the local government to begin the process. The detailed discussions of the funding scheme with the local government are currently on-going since two major changes of the operating conditions occurred in this first year of activities of MIA-Portugal. First, there was a delay in the final decisions on the configuration of European support funds for this new decade, likely as a result of the pandemics. Second, there was a change of President of the local government since the former president was invited to become a minister of the Portuguese government, and a natural lag time was required for the new president to become acquainted with all the process. Thanks to the full alignment of all stakeholders, we are confident to begin the construction of the building this year, a process that we expect to be completed within 3 year, well in time to host all the research groups of MIA-Portugal.

This time required to have the new research building ready imposes the need to provide provisional facilities for the currently hired two first groups of MIA-Portugal to begin their activities. The strategy is to hook the laboratory facilities provided to the two hired groups to laboratory facilities of an established research group, ensuring a smoother and faster integration of activities of the new groups with all pre-existing facilities. The localization for the new facilities, in the close vicinity of the Center for Neuroscience and Cell Biology were identified by the Faculty of Medicine and by the Rectory of the University of Coimbra. The architectural and engineering plan of the required re-building was completed and approved in late January and the rectory was informed of the investment required for basic equipment to have these new laboratory facilities operational. However, the full engagement of all engineering teams of the University in the rebuilding of the new Laboratory for Sars-Cov2 screening precluded any possibility of initiating the intervention this year. The rebuilding has now started and is expected to be ready within 3 months, fully equipped to receive the two hired PIs of MIA-Portugal.

4-<u>Scientific activities of support groups of MIA-Portugal</u>:

Although research activities at MIA-Portugal will formally be launched by the newly recruited research teams, the strategy of installation of MIA-Portugal is defined to imbed the newly recruited groups in a pre-existing scientific activity by groups already settled at the University of Coimbra. In this respect, some research groups led by researchers formally attached to the implementation of MIA-Portugal, have been consistently producing scientific knowledge related to ageing and age-related chronic diseases, as briefly summarized below:

Lino Ferreira, holder of the ERA-Chair@UC on Ageing has continued his efforts to unravel mechanisms of vulnerability associated with ageing and exploiting novel delivery systems to bolster the selectivity and efficiency of drug delivery, as testified by the following publication:

Pitrez PR, Estronca L, Monteiro LM, Colell G, Vazão H, Santinha D, Harhouri K, Thornton D, Navarro C, Egesipe AL, Carvalho T, Dos Santos RL, Lévy N, Smith JC, de Magalhães JP, Ori A, Bernardo A, De Sandre-Giovannoli A, Nissan X, Rosell A, Ferreira L (2020) Vulnerability of progeroid smooth muscle cells to biomechanical forces is mediated by MMP13. Nat Commun 11:4110. doi: 10.1038/s41467-020-17901-2.

Ferreira R, Napoli J, Enver T, Bernardino L, Ferreira L (2020) Advances and challenges in retinoid delivery systems in regenerative and therapeutic medicine. Nat Commun 11:4265. doi: 10.1038/s41467-020-18042-2.

de Abreu RC, Fernandes H, da Costa Martins PA, Sahoo S, Emanueli C, Ferreira L (2020) Native and bioengineered extracellular vesicles for cardiovascular therapeutics. Nat Rev Cardiol 17:685-697. doi: 10.1038/s41569-020-0389-5.

In parallel, the group of Claudia Cavadas has continued to pursue the therapeutic potential of targeting neuropeptide Y signaling to control senescence:

Aveleira CA, Ferreira-Marques M, Cortes L, Valero J, Pereira D, Pereira de Almeida L, Cavadas C (2020) Neuropeptide Y enhances progerin clearance and ameliorates the senescent phenotype of human Hutchinson-Gilford progeria syndrome cells. J Gerontol 75:1073-1078. doi: 10.1093/gerona/glz280.

The group of Rodrigo Cunha detailed the role of adenosine A_{2A} receptors as triggers of neuronal maladaptive features upon ageing and exploited the potential of targeting these A_{2A} receptors to bolster brain metabolism and control neurodegenerative diseases such as Parkinson's disease:

Temido-Ferreira M, Ferreira DG, Batalha VL, Marques-Morgado I, Coelho JE, Pereira P, Gomes R, Pinto A, Carvalho S, Canas PM, Cuvelier L, Buée-Scherrer V, Faivre E, Baqi Y, Müller CE, Pimentel J, Schiffmann SN, Buée L, Bader M, Outeiro TF, Blum D, Cunha RA, Marie H, Pousinha PA, Lopes LV 2020) Age-related shift in LTD is dependent on neuronal adenosine A_{2A} receptors interplay with mGluR5 and NMDA receptors. Mol Psychiatry 25:1876-1900. doi: 10.1038/s41380-018-0110-9.

Aguiar AS Jr, Speck AE, Canas PM, Cunha RA (2020) Neuronal adenosine A_{2A} receptors signal ergogenic effects of caffeine. Sci Rep 10:13414. doi: 10.1038/s41598-020-69660-1.

Chen JF, Cunha RA (2020) The belated US FDA approval of the adenosine A_{2A} receptor antagonist istradefylline for treatment of Parkinson's disease. Purinergic Signal 16:167-174. doi: 10.1007/s11302-020-09694-2.

The group of Cristina Rego further advanced our knowledge on the relation between metabolic dysfunction and neurogenesis in the realm of Alzheimer's disease:

Ferreiro E, Lanzillo M, Canhoto D, Carvalho da Silva AM, Mota SI, Dias IS, Ferreira IL, Fontes AR, Mastrella G, Pinheiro P, Valero J, Rego AC (2020) Chronic hyperglycemia impairs hippocampal neurogenesis and memory in an Alzheimer's disease mouse model. Neurobiol Aging 92:98-113. doi: 10.1016/j.neurobiolaging.2020.04.003.

Finally, the group of Carlos Palmeira expanded the association of metabolic controllers, such as sirtuin-3 or sestrin-2, to ageing features:

Gomes P, Viana SD, Nunes S, Rolo AP, Palmeira CM, Reis F (2020) The yin and yang faces of the mitochondrial deacetylase sirtuin 3 in age-related disorders. Ageing Res Rer 57:100983. doi: 10.1016/j.arr.2019.100983.

Oliveira RP, Machado IF, Palmeira CM, Rolo AP (2020) The potential role of sestrin 2 in liver regeneration. Free Radic Biol Med 163:255-267. doi: 10.1016/j.freeradbiomed.2020.12.027.

Apart from these scientific outputs, efforts were made to strengthen the links between MIA-Portugal and our supporting partners, as heralded by a joint research project submitted by Claudia Cavadas and Thomas von Zglinicki to the Portuguese Science Foundation. Furthermore, the European program Spreading Excellence and Widening Participation promoted by Horizon 2020 awarded the project RESETaging to Lino Ferreira, financed in the twinning category, with the aim of investigating in the area of cardiovascular aging, a project involving collaborative activities with the University of Newcastle (UK).

In spite of these supportive activities and of the evidence for emerging collaborative efforts with our supportive partners, the inexistence of autonomous funds was a truly lost opportunity to exploit the importance of ageing in the lethality of covid in the elderly population. In fact, the University funding was mostly, and logically, directed to routine screening efforts and the project MIA-Portugal lacks funding tools to exploit the tremendous research opportunities offered by this pandemic.

5-<u>Hiring of the Scientific Director of MIA-Portugal</u>:

The process of hiring the Scientific Director of MIA-Portugal is a critical step to go from implementation to functioning of MIA-Portugal. The project anticipated a period of 18 months to complete this key deliverable. We certainly encountered major unexpected hurdles to speed this process. In fact, the limitations to traveling and the cancelation of most scientific meetings, which are paramount to establish, renew and strength personal contacts with potential candidates, hampered the efforts to enlist potential candidates. We are also fully aware of the difficulty of this task due to differences in salaries at Universities between Portugal and other Western countries, in spite of attractiveness of the project and the cost and quality of life in Coimbra. All team members and partners are making all efforts to identify possible candidates. It is worth mentioning the commitment of the Dean of the University championing these efforts with a remarkable personal involvement in establishing promising contacts with some valuable candidates. The commitment of the Dean to resolve this process is further heralded by the successful efforts to link this position to that of a permanent position created within the University, namely within the Faculty of Medicine that hosts several planned activities of MIA-Portugal project. This new framework made possible by the direct commitment of the Dean makes us confident that we may successfully achieve the completion of this goal within the expected timeframe.

6-<u>Teaching activities with partners of MIA-Portugal</u>:

Although MIA-Portugal project included a strategy for the implementation of several activities directed at adequately preparing the next generation of stakeholders involved in the amelioration of the health status of the population, different opportunities evolved in this area with the active participation of members of the consortium. In particular, the approval

of the project Ageing@ EITHealth_Brain PhD School is an important step to begin responding to this need. Therefore, MIA's strategy is obviously to join rather than to duplicate efforts. Accordingly, members of the consortium participated in the virtual Annual Retreat of the students of the EIT Health Ageing PhD School, which was held from November 30th to December 4th, 2020. MIA-Portugal will continue to actively support this endeavor and is looking forward to increasingly participate in the activities of this graduate training instrument.

7-Clinical and commercial partnerships:

The establishment of clinical and commercial partnership will be paramount for the long-term sustainability of MIA-Portugal. We are all aware that it is never too early to begin constructing opportunities to achieve this goal. Our internal plan was composed of a three-steps strategy to maximize opportunities: first a general outreach of the scope of planned activities of MIA-Portugal, then a continuous information of achievements of MIA-Portugal deemed of interest for future partnerships and finally the direct quest for focused meetings to prepare such partnerships. While there is no scientific activity to support the genesis of new knowledge, we planned in this first year of activities to start disseminating MIA-Portugal to a list of companies from various branches identified as potential future partners of MIA-Portugal. However, the current economic crisis resulting from the COVID pandemic led to a re-focus of attention of most companies, from investment planning for long-term growth to adaptive strategies for short-term survival. Thus, we focused on exploring initial contacts with some multinationals with sufficient dimension to buffer the current general economic retraction. Even for these companies, despite the perceived receptivity in terms of potential interest, a retraction in the assumption of longer term commitments is evident. We maintain our hope that with some tangible results derived from the initiation of the activities of MIA-Portugal, we will bolster our effectiveness to raise the interest of commercial future partners.

As for clinical activity or partnerships, no activity was even attempted given the near sole focus of Hospitals in dealing with the COVID pandemic.

8-Outreach program:

The current general focus of the public opinion on COVID pandemic dampens the usefulness of efforts to raise interest in public or specialized audiences on any other topic. Furthermore, outreach activities either to the lay audiences or specialized audiences were made difficult by the rules limiting public gatherings and by the cancelling of the vast majority of scientific meetings. Finally, the tremendous economic burden imposed by the pandemic on companies shifted their attention to survival rather than to the establishment of long-term partnerships. Thus, in general, outreach efforts would mostly be vain efforts with anticipated little reward.

The main strategies to support outreach activities also need to be reconsidered at present. Whereas the pre-pandemic strategy involved the support of written material to be distributed and exploited with different audiences, the current pandemic imposes a preference for long distance communication strategies. We have already completed the hiring selection of the communication officer (among 60 candidates) to coordinate all these efforts, encompassing both press releases and managing of digital contents with emphasis on video material. The selected candidate will hopefully start this process in February.

We are fully aware that outreach activities for the general public and potential partners is paramount for the success of the implementation of MIA-Portugal and especially for the long-term sustainability of this endeavor. It was probably the most severely affected set of activities in this atypical year. And, with that in mind, it will be one of the priorities for the planned activities in this next year of implementation of MIA-Portugal: we have created the conditions and understood the limitations, we now hope to rapidly implement an efficient strategy to publicize the scope of MIA-Portugal and the opportunities offered for partnerships.

Final remarks:

In spite of the limitations imposed by the current pandemic, all the milestones planned for this first year of activities of MIA-Portugal project were successfully completed. Thus, the bylaws and managing structures of MIA-Portugal are in place and the first two Principal investigator of MIA-Portugal were selected, both of truly outstanding quality. Although presential contacts have been severely restrained by the pandemic thus limiting our efforts to identify relevant candidates, the hiring of the Scientific Director is also evolving thanks to the efforts and the commitment of the Dean. Important steps were achieved in the implementation of MIA-Portugal facilities, although we are fully aware that the process could have been faster without deviation of efforts to priority health care needs imposed by the pandemics. Finally, we have set in place the person in charge to coordinate the communication of MIA-Portugal prompting the mandatory condition to begin an effective outreach program of activities, necessarily adapted to the constraints of the current pandemic. In summary, we maintain our confidence in the successful implementation of MIA-Portugal project.