



Lino Ferreira, Project Coordinator, University of Coimbra

Dear RESETageing partners:

It is my pleasure to share with you the sixth and last RESETageing newsletter. In this newsletter we do an overview of the RESETageing activities performed during the project. We also talk about the outreach activities that RESETageing researchers have been involved since the previous newsletter.

I want to thank all the members of the consortium that during the course of the project contributed for the success of RESETageing project

Best wishes

Lino

Alessandro Ori - Leibniz Institute on Aging Coordinator

The last three years of RESETageing have been an incredibly enriching and inspiring experience. We have been very enthusiastic to pick the challenge to organize a virtual summer school during the difficult times of COVID and to be able to host other members of the consortium in Jena. Many of us enjoyed the scientific exchanges of the RESETageing conferences and several students benefited from the training opportunities. On the scientific side, it has been very exciting to use our advanced proteomic platform to study how remodeling of the extracellular matrix contribute to heart aging and to reveal mechanistic insights on the mechanism of action of senolytics on cardiomyocytes. We look forward to see how new project emerging from RESETageing will contribute to the advancement of aging research in Europe.

Viktor Korolchuk - Newcastle University Coordinator

RESETageing provided an invaluable platform for building new collaborations and supporting existing links between Newcastle and European centres working on ageing. Annual meetings, training schools and short-term exchange visits allowed for the initiation of several collaborative research projects. Outcomes from some of these have already been published, but even more importantly RESETageing will lead to a long-term cooperation between institutions and individual groups. So far, the progress made within the scientific cooperation framework established novel mechanisms of senescence related to cardiac function and ways to counteract them. These results will underpin years of our future joint research with an ultimate goal to identify potent anti-ageing interventions.

Paula da Costa Martins - University of Maastricht Coordinator

ResetAgeing contributed to our understanding and approach to the ageing process. By uniting researchers, healthcare professional and technology experts at different stages of their careers, the consortium was able to identify and establish new mechanisms of ageing related to specific diseases. The way the consortium brought together experts from different disciplines, cutting-edge laboratories and biobanks, facilitated high-quality research and provided an excellent networking platform for younger researchers in training, empowering them to build robust professional networks, advance their career prospects while contributing to ageing research. The Annual meetings, training schools and short-term exchange visits were crucial for fostering interdisciplinary collaborations, securing funding and disseminating research findings within the consortium, and in particular for us, boost the connection between the University of Maastricht and other European groups working on ageing research.

RESETageing Conferences

RESETageing organized three international conferences opened to the scientific community during the project having overall 410 participants, promoting interaction and networking with international experts in ageing research within and also outside the consortium.

The first conference (11th June, 2021) was forced to be virtual due to Covid Pandemics restrictions, but even in this hard period we manage to organize an international conference with high quality and with a massive participation (240 registrations!), showing the motivation and perseverance of all RESETageing partners to achieved the purposed goals of the project. The conference cover several topics, from Cell Senescence (Manuel Serrano, Marco Demaria), to Omics of Ageing (João Pedro Magalhães, Alessandro Ori), to Cardiovascular Ageing (Gavin Richardson, Leon de Windt, Manuel Mayr, Jordan Miller), Telomeres and Mitochondria Dysfunction (Miguel Godinho, Laura Greaves, João Passos) and Emerging Concepts in Ageing (Adam Engler, Johannes Grillari, Anna O'Loghlen, Daniel Munoz-Espin).

The second conference (16th and 17th September, 2022) was organized in Newcastle and was attended by 60 participants. In this day and a half conference several topics were covered: Ageing: from model systems to humans Cell Senescence (Adam Antebi, Miles Witham), Biology of Ageing (Dudley Lamming, Henrique Girão), Mechanisms of Ageing (Vera Gorbunova, Alberto Sanz), Senescence and Ageing (Masashi Narita, Satomi Miwa), Molecular turnover in Ageing (David Vilchez, Ira Milosevich) to age-related disease and anti-ageing interventions (Paula da Costa Martins). There were 15 short communications selected from abstracts and a poster session which enhanced the discussion and proximity between junior and senior expert researchers in the area of ageing promoting networking between the consortium.

In the third conference (6th and 7th December, 2023), organized in Coimbra, we manage to gather almost the double of participants (about 110) from the previous conference. This outstanding participation is indicative of the quality of RESETageing conferences in the thematic of ageing. We had a fantastic poster session with about 40 scientific posters, 6 keynote lectures and 15 presentations on the following thematics: Biology of Ageing (Jesus Gil, Claudia Cavadas, Viktor Korolchuk, Cristina Rego, Nuno Raimundo), Cardiovascular Ageing (Ian Guldner, Susana Rosa, Lenhard Rudolph, Vicente Andrés, Diana Nascimento, Bruno Jesus, Gavin Richardson), Interventions to prevent or reverse ageing (Fabrisia Ambrosio, Elsa Logarigno, Alberto Minetti, Consuelo Borrás, Ramón Martínez-Mñez, Vitor Francisco, Ana O'Loghlen). A video was recorded during the last conference which can be seen [here](#)

We want to thank to all the participants the contribution for the fantastic conferences.



RESETageing Training

One of the specific objectives of RESETageing project was the increase teaching and training quality in ageing and on top of the 3 international conferences, 3 specially designed training schools were successfully organized by the consortium involving a total of 59 students from all partners of the consortium and a Workshop in Innovation and Business Ignition program in ageing involving 13 students selected from the consortium.

Starting with a training school in Gene and Proteomic analysis (organized by Alessandro Ori, LIA, June 2021), followed by a training in Single cell techniques in senescence and ageing (organized by Satomi Miwa and Viktor Korolchuk, UNEW, September 2022) and finally a training on Super-Resolution Microscopy (organized by Lino Ferreira, UC, December 2023). All training schools gather very good feedback from the students which acquired skills in the different thematics to use in their research. We want to thank to all the contribution for the training schools.



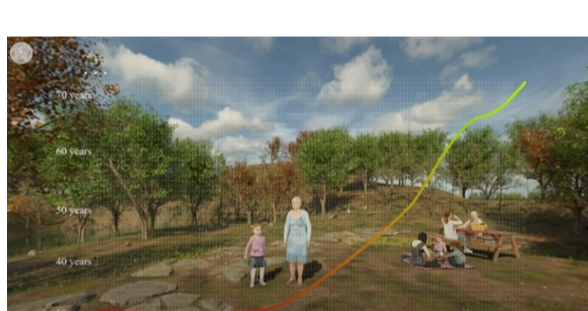
The 2 week workshop occurred in January 2023 and was organized by University of Coimbra and Instituto Pedro Nunes. Students were divided in 4 groups and each had to develop a new product/ service based on a specific technology. During the workshop students learn the creation of Go to Market plans from scratch and at the end performed a Pitch of their technology to a jury. It were 2 intense weeks but the hard work and determination of the students was evident by the high quality work developed and their Pitches. A video of this event was created and can be seen [here](#)



During the course of the project the exchange of members within RESETageing consortium was strongly encouraged to foster collaborations between partners, particularly of Master and PhD students such as Andreia Vilaça, Ricardo Abreu, Deolinda Santinha, Raquel Videira, Inês Tomé, Tade Idowu, Rita Sá Ferreira, Raíaela Ferrão, Carolina Mendes, Andreia Marques, Joana Padrão, Simão Santos, João Novo, Francesca Tomatis, Maria Cardoso, Daniela Marinho, Beatriz Martins, Niall Wilson, Tornike Nasrashvili, Jordy Kocken, Martin Bagic, Joana Alves da Silva, benefit from RESETageing project exchange.

Outreach Activities

RESETageing project was disseminated in several outreach activities for public engagement and science communication during all project. A virtual reality video entitled "A closer look to the aging process" was elaborated (the full video can be visualized [here: A closer look to the aging process](#)). The video shows at the cellular level what happens when people aged, how does this phenomenon happen throughout life and how to promote a healthy aging. In all the activities were this virtual reality video was show to the public had a fantastic feedback, from children to adults



We were present at the European Researchers' Night 2021, 2022, 2023, Brain Fair 2022, Pic'N'com Saúde, FIC.A International Science Festival.

RESETageing was also present at Portuguese schools where collaborators discussed with students about ageing and highlight activities to promote an healthy ageing.



May 2024



Publications

Below is a list of 19 publications (some are in the preparation or submission process) produced during RESETageing project. We want to highlight that all journals are quartil Q1, showing the high productivity and particularly the high quality of the work developed by RESETageing collaborators within the project.

Involving 1 RESETageing partner

- 1) Silva ED*, Tomé I*, Vasques-Nóvoa F, Conceição G, Silva A, Barros A, Gonçalves A, Caetano C, Sousa D, Silva D, Nádia, Pinto VP, Alexandre, Moreira AL, Pires IF, Pitrez P, Pinto-do-Ó P, Santos SG, Ferreira L#, Nascimento DS#. Pharmacological clearance of senescent cells with Navitoclax reverses HFpEF hallmarks by decreasing inflammation, endothelial dysfunction and cardiac fibrosis. *Cardiovascular Research* 2024 (submitted)
- 2) Simoes, S, Lino, M, Barrera, A, Rebelo, C, Tomatis, F, Vilaça, A, Breunig, C, Neuner, A, Peça, J, Gonzalez, R, Carvalho, A, Stricker, S, Ferreira, L. Near infrared light-activated formulation for the spatial controlled release of CRISPR-Cas9 ribonucleoprotein for brain gene editing. *Erwandte Chemie* 2024, 63, e202401004. Doi: 10.1002/anie.202401004.
- 3) Banerjee A, Lino M, Jesus C, Ribeiro Q, Abrunhosa A, Ferreira L. Imaging platforms to dissect the in vivo communication, biodistribution and controlled release of extracellular vesicles. *J Control Release*. 2023 Aug;360:549-563. doi: 10.1016/j.jconrel.2023.06.039
- 4) Rebelo C, Reis T, Guedes J, Saraiva C, Rodrigues AF, Simões S, Bernardino L, Peça J, Pinho SL, Ferreira L. Efficient spatially targeted gene editing using a near-infrared activatable protein-conjugated nanoparticle for brain applications. *Nat Commun*. 2022 Jul 16;13(1):4135. doi: 10.1038/s41467-022-31791-6
- 5) Martins-Marques T, Costa MC, Catarino S, Simoes I, Aasen T, Enguita FJ, Giroa H. Cx43-mediated sorting of miRNAs into extracellular vesicles. *EMBO Rep*. 2022 Jul 5;23(7):e54312. doi: 10.15252/embr.202154312
- 6) Marinho D, Ferreira IL, Lorenzoni R, Cardoso SM, Santana I, Rego AC. Reduction of class I histone deacetylases ameliorates ER-mitochondria cross-talk in Alzheimer's disease. *Aging Cell*. 2023 Aug; 22(8):e13895. doi: 10.1111/ace.13895.
- 7) Redgrave RE, Dookun P, Passos JF, Rickard, Camacho Encina M, Folaranmi O, Tual-Chalot S, Gill JH, Owens WA, Spyridopoulos I, Pannos B, Othman GD. Senescence cardiomyocytes contribute to cardiac dysfunction following myocardial infarction. *NPJ Aging*. 2023 Jun 14;9(1):15. doi: 10.1038/s41514-023-00113-5.
- 8) Silva J, da Costa Martins PA. Non-Coding RNAs in the Therapeutic Landscape of Pathological Cardiac Hypertrophy. *Cells*. 2022 May 31;11(11):1805. doi: 10.3390/cells11111805. PMID: 35681500; PMCID: PMC9180404.
- 9) Juni RP, Kocken JMM, Abreu RC, Ottaviani L, Davalan T, Duygu B, Poels EM, Vasilevich A, Hegenbarth JC, Appari M, Bitsch N, Olieslagers S, Schrijvers DM, Stoll M, Heineke J, de Boer J, de Windt LJ, da Costa Martins PA. MicroRNA-216a is essential for cardiac angiogenesis. *Mol Ther*. 2023 Jun 7;31(6):1807-1828. doi: 10.1016/j.ymthe.2023.04.007.

Involving 2 or more RESETageing partner

- 10) Vilaça A, de Windt LJ, Fernandes H, Ferreira L. Strategies and challenges for non-viral delivery of microRNA-216a to the heart. *Trends Mol Med*. 2023 Jan;29(1):70-91. doi: 10.1016/j.molmed.2022.10.002.
- 11) de Abreu RC, Ramos CV, Becher C, Lino M, Jesus C, da Costa Martins PA, Martins PAT, Moreno MJ, Fernandes H, Ferreira L. Exogenous loading of miRNAs into small extracellular vesicles. *J Extracell Vesicles*. 2021 Aug;10(10):e12111. doi: 10.1002/jev2.12111.
- 12) Ottaviani L, Juni RP, de Abreu RC, Sansonetti M, Sampaio-Pinto V, Halkein J, Hegenbarth JC, Ring N, Knoops K, Kocken JMM, Jesus C, Ernault AC, El Azzouzi H, Rühle F, Olieslagers S, Fernandes H, Ferreira L, Braga L, Stoll M, Nascimento DS, de Windt LJ, da Costa Martins PA. Intercellular transfer of miR-200c-3p impairs the angiogenic capacity of cardiac endothelial cells. *Mol Ther*. 2022 Jun 1;30(6):2257-2273. doi: 10.1016/j.ymthe.2022.03.002.
- 13) Fernandes H, Zonnari A, Abreu R, Aday S, Barão M, Albino I, Lino M, Branco A, Seabra C, Barata T, Leal EC, Ferreira L, Gonçalves L, de Jong A, Peters H, de Vries MR, da Costa Martins PA. Quax PHA, Ferrihã L. Extracellular vesicles of enriched with an endothelial cell pro-survival microRNA protect skin tissue regeneration. *Mol Ther Nucleic Acids*. 2022 Mar 19;28:307-327. doi: 10.1016/j.omtn.2022.03.018.
- 14) Kelly G, Kataura T, Panek J, Ma G, Salmonowicz H, Davis A, Kendall H, Brookes C, Ayine-Tora DM, Ferreira P, Nelson G, Dobzy-Lopez PR, Booth L, Costello L, Richardson GD, Flavag P, Przyborski J, Banks R, Greaves L, Szczepanowska K, von Zglinicki T, Miwa S, Brown M, Flotter M, Oblongk SE, Bascom CC, Carroll B, Reynisson J, Korolchuk VI. Suppressed basal mitophagy drives cellular aging phenotypes that can be reversed by a p62-targeting small molecule. *Dev Cell*. 2024 May 20;51534-5807(24):00295-8. doi: 10.1016/j.devcel.2024.04.020.
- 15) Andreia Vilaça, A, Jesus C, Lino, M, Hayman D, Emanuel C, Terracciano CM, Fernandes H, de Windt LJ, Ferreira L. Extracellular vesicle transfer of lncRNA H19 splice variants to cardiac cells. *Mol Ther Nucleic Acids*. 2024 Published:online June 02, 2024 doi:10.1016/j.omtn.2024.102233
- 16) Santinha D, Vilaça A, Estronca L, Schüler SC, Bartoli C, De Sandre-Giovannoli A, Figueiredo A, Quas M, Pompe T, Ori A, Ferreira L. Remodeling of the Cardiac Extracellular Matrix Proteome During Chronological and Pathological Aging. *Mol Cell Proteomics*. 2024 Jan;23(1):100706. doi: 10.1016/j.mcp.2023.100706.
- 17) Tomatis, F, Rosa, S, Simões, S, Barão, M, Barth, E, Marz, M, Ferreira, L. "Engineering extracellular vesicles to permeabilize the blood-brain barrier". *J Nanobiotechnology* 2024 (submitted)
- 18) Novo, JP, Gee, L, Caetano, AC, Tomé, I, Vilaça, A, Zglinicki, T, Moreira, IS, Jurk, DS, Rosa, S, Ferreira, L. "Blood-brain barrier dysfunction in ageing is mediated by brain endothelial senescence". *Aging Cell* 2024 (accepted for publication)
- 19) Luís M. Monteiro, Simão C. Santos, Nicola Dark, Deolinda Santinha, Vilma Sardão, Luísa Cortes, Rui Ribeiro, James C. Smith, Anders Nissan, Alessandro Ori, Elsa Logarigno, Andreia Bernardo, Patrícia R. Pitrez*, Lino Ferreira*. "Modeling progeria in cardiomyocytes derived from human induced pluripotent stem cells." (In preparation).

FINAL REMARKS

Publications or presentations resulting from work developed under the scope of RESETageing have to include the following sentence and the EU flag: "This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 952266".

RESETageing official LOGO

We kindly ask all the members of RESETageing consortium to use this logo whenever RESETageing project is mention.

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