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Deadline: March 1st, 2024

EUR CARe PhD program pre-proposal

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Research project title: ATPase Inhibitory factor 1 (IF1) in energy metabolism and aging

Research program abstract (*P1*, Martinez; *P2*, Croyal; *P3*, Ferrucci)

Rationale

Impairment of mitochondrial function with age leads to energy deficits and oxidative stress that are early indicators of failing health, even before diseases become apparent (PMID:36371805, *P1*). Thus, understanding and characterizing the biological actors and pathways involved in mitochondrial bioenergetics are essential for identifying biomarkers and therapeutic targets that are causally associated with age-related functional decline (PMID:38355974, *P3*).

State of the art

The ATPase Inhibitory Factor 1 (IF1) is a nuclear-encoded endogenous inhibitor of the mitochondrial ATP synthase. Recent findings, including ours, highlight IF1's emerging role in regulating mitochondrial bioenergetics and metabolite production (PMID:34605675, *P1*)

First, during physiological oxidative phosphorylation, IF1 induces mitochondrial hyperpolarization by restraining ATP synthesis, shifting energy metabolism towards increased glycolysis.

Secondly, IF1 modulates the production of mitochondria-derived products, including mitochondrial reactive oxygen species (mROS).

Thirdly, from a clinical perspective, *P1* and *P2* were the first to identify IF1 in human plasma as a mitochondrial-secreted biomarker (PMID:32887042, *P1* & *P2*). As part of the IHU HealthAge, *P1* and *P2* found that plasma IF1 levels in the elderly correlated with physical activity and intrinsic capacity (IC), a measure reflecting healthy aging (PMID:37748689 37280149, *P1*).

These findings heighten interest in **IF1 as a circulating biomarker of energy deficiency in mitochondria and pharmacological target**. However, IF1's contribution to mitochondrial dysfunction in aging remains to be evaluated.

Research hypothesis and Project's objectives

Given the state of the art, ***our hypotheses are*:**

- Mitochondrial IF1 favors mitochondrial dysfunction and age-related functional decline.
- Plasma level of IF1 is possibly a proxy of mitochondrial energy metabolism and a potential biomarker of aging.

Project's objectives consist of 2 parts:

- **Part 1. Basic research**: *To analyze IF1 deficiency on multi-organ functional reserve during aging.*
- **Part 2. Translational research**: *To validate IF1 as a biomarker of aging.*

Methodology

- Part 1: In 6- and 24 months male and female IF1 deficient mice (IF1 KO), available in the *P1* laboratory, functional and biological phenotypes will be analyzed compared to control mice. These analyses will include energy balance (using PhenoMaster), endurance, resistance (treadmill), gait/frailty, and memory (PMID:33575700, *P1*). Initial findings suggest that IF1 KO mice exhibit improved locomotion and endurance. Furthermore, multi-organ phenotyping, including liver, brain, and muscles, will be assessed through an OMIC-approaches involving metabolomics and lipidomics (led by *P2*), and proteomics and transcriptomics (led by *P3* during internship). *P3* will also supervised and trained to advanced computational analyses of OMICs, including mRNAs clustering and pathway analyses, to identified OMICs signatures, considering IF1 deficiency as an model of optimal ATP synthase activity.

- Part 2: Plasma IF1 will be measured (led by *P2*) in the Baltimore Longitudinal Study in Aging (BLSA, PMID:32196924, *P3*). Several association analyses will be conducted with clinical and biological characteristics of the cohort study. These biostatistics analyses, supervised by *P3* during the internship, will examine the correlation between IF1 and (31)P-MRS measurements of mitochondrial oxidative capacity in muscle. Additionally, multivariate regression analyses will be conducted to assess the prognostic value of IF1 in predicting longitudinal changes in health trajectories.

Describe in 50 words max for each how this project fits the 3 defining criteria of the CARe graduate programme:

1) Relation to CARe topics of Cancer, Ageing and/or Rejuvenation

This project directly addresses ageing-related issues by investigating the role of ATPase Inhibitory Factor 1 (IF1) as a biomarker and target in mitochondrial dysfunction during functional decline in ageing.

2) Multidisciplinary aspect

The project integrates various disciplines, including age-related physiology in mice (*P1*), OMICs (*P2,* utilizing LC-MS/MS & *P3*), computational analyses (*P3*), and biostatistics in a human cohort (*P3*). This aims to comprehensively study IF1's impact on multi-organ functional reserve during aging and its underlying biology, bridging fundamental research with translational applications.

3) International and/or industrial aspect(s)

The project relies on co-supervision with NIA (L.Ferrucci, USA, *P3*) and the Institut du Thorax (*P2*), both training the candidate in OMICS techniques. During the internship, *P3* will provide training in computational analyses of OMICS data and statistical analyses on BLSA cohort, potentially leading to biomarker validation and industrial translation.

5 keywords in line with EUR CARe

Mitochondrial Bioenergetics, Functional reserve, multi-organ decline, Health Trajectories, ageing biomarker.

5 references of the teams, highlighting the co-signatory students

***Last 5 years,* Partner contribution is indicated into bracket (P1, P2, P3) :**

1) Raffin J, Rolland Y, Genoux A, Combes G, Croyal M, Perret B, Guyonnet S, Vellas B, Martinez LO, de Souto Barreto P; MAPT/DSA Group. Associations between physical activity levels and ATPase inhibitory factor 1 concentrations in olderadults. *J Sport Health Sci.* 2023 Sep 23:S2095-2546(23)00094-7. doi:10.1016/j.jshs.2023.09.009. PMID: 37748689. (*P1*, *P2*).

2) da Silva JA, Martinez LO, Rolland Y, Najib S, Croyal M, Perret B, Jabrane-Ferrat N, El Costa H, Guyonnet S, Vellas B, de Souto Barreto P; MAPT/DSA group. Plasma Level of ATPase Inhibitory Factor 1 and Intrinsic Capacity in Community-Dwelling Older Adults: Prospective Data From the MAPT Study. *J Gerontol A Biol Sci Med Sci.* 2024 Jan 1;79(1):glad142. doi: 10.1093/gerona/glad142. PMID: 37280149. (*P1*, *P2*).

3) Mérian J, Ghezali L, Trenteseaux C, Duparc T, Beuzelin D, Bouguetoch V, Combes G, Sioufi N, Martinez LO, Najib S. Intermittent Fasting Resolves Dyslipidemia and Atherogenesis in Apolipoprotein E-Deficient Mice in a Diet-Dependent Manner, Irrespective of Sex. *Cells.* 2023 Feb 7;12(4):533. doi:10.3390/cells12040533. PMID: 36831200. (*P1*).

4) Genoux A, Duparc T, Ruidavets JB, Ingueneau C, Najib S, Ferrières J, Perret B, Croyal M, Martinez LO. A reference measurement of circulating ATPase inhibitory factor 1 (IF1) in humans by LC-MS/MS: Comparison with conventional ELISA. *Talanta.* 2020 Nov 1;219:121300. doi: 10.1016/j.talanta.2020.121300. PMID: 32887042. (*P1*, *P2*).

5) Adelnia F, Ubaida-Mohien C, Moaddel R, Shardell M, Lyashkov A, Fishbein KW, Aon MA, Spencer RG, Ferrucci L. Proteomic signatures of in vivo muscle oxidative capacity in healthy adults. *Aging Cell.* 2020 Apr;19(4):e13124. doi: 10.1111/acel.13124. PMID: 32196924. (*P3*).