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Deadline: February 27th, 2026

EUR CARe PhD program pre-proposal

(2 pages maximum)

PhD Director:
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PhD co-Director:
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PhD co-Director affiliation:
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Research project title:
Conserved Transcriptional Regulators during Ageing Transitions: From Flies to Humans.

Research program abstract (max 500 words):

Ageing is highly variable within a population: individuals differ markedly in the onset and severity of functional decline. In humans, the genetic contribution to this variability is modest (~15–30%), highlighting a major role for **non-genetic, stochastic processes** such as cumulative micro-damage that can erode robustness and trigger tipping points toward frailty.

A central question is what molecular changes precede and drive these transitions. Tissue adaptation to stress and homeostasis rely on precise differential gene expression, controlled by transcriptional **gene regulatory networks (GRNs)**. We hypothesize that stochastic damage progressively perturbs GRN organization, leading either to **adaptive drift** (coordinated, compensatory shifts) or to **disorganization** (loss of coordination and rewiring), thereby increasing stress sensitivity; recurrent GRN motifs may forecast tipping points.

Consistent with non-linear transitions, longitudinal human transcriptomic analyses report **two major waves of molecular change** around the mid-40s (~42–45 years) and later life (~60 years), suggesting shifts in regulatory programs at defined transition periods.

Drosophila melanogaster is uniquely suited to dissect GRN dynamics in vivo using tissue-specific genetic tools. In our *Drosophila* framework we have identified **two reproducible tipping points (~day 20; ~day 40)**: ~day 20, marked by a sharp locomotor decline without detectable survival cost, and ~day 40, followed by a major survival collapse. Inter-individual variability rises strongly after day 20 and peaks before the late-life transition, defining a heterogeneous pre-frail phase. **This heterogeneity is central to our approach** and motivates single-fly profiling rather than population averages.

This PhD program will use **tissue-specific, single-fly omics based on DamID** to capture population heterogeneity across both tipping points in two key tissues—**muscle and fat body**—and reconstruct GRNs at individual resolution. By profiling large numbers of individuals (~100–200 per time point, using barcoding/multiplexing), we will quantify variation at the GRN level and test whether recurrent GRN states

emerge. In parallel, the laboratory is running a targeted genetic screen, functionally testing a curated panel of **~50–100 transcription factors (TFs)**—prioritized for human/fly orthology and **conserved age-associated expression** by intersecting age-variable TFs from the *Drosophila* ageing single-cell atlas with human aging transcriptomic datasets—to identify the few TF hits that modulate the timing and/or severity of the *Drosophila* tipping points. These hits will serve as **functional anchors for network inference** and interpretation.

International partnership / multidisciplinarity: A central and indispensable component is the co-supervision with **Dr Norbert Perrimon (Harvard Medical School)**, including a **3–6-month internship**. This partnership is essential to bridge in vivo ageing biology in Toulouse with **large-scale GRN inference and quantitative network modelling** in Boston. Dr Perrimon's group brings state-of-the-art expertise in scalable functional genomics and in extracting regulatory structure from high-dimensional datasets. Together, we will reconstruct tissue- and individual-resolved GRNs, and develop **new quantitative metrics (not off-the-shelf pipelines)** to measure GRN disorganization/deregulation across individuals and tipping points, distinguish adaptive drift from loss of coordination, and model divergent ageing trajectories. Dr Perrimon will be engaged throughout the PhD via joint meetings every 2–3 months, providing continuous guidance on experimental design, analysis strategy, and interpretation.

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 aligns with CARe's Ageing axis by explaining why individuals within a population age differently. It connects frailty onset and tipping points to changes in gene regulatory networks (GRNs), mapped at single-individual resolution in fat body and muscle, to identify predictive signatures of functional decline.

2) **Multidisciplinary aspect:** The project is inherently multidisciplinary: it couples in vivo ageing experiments in Toulouse with **method development in network science**. Single-fly multi-omics will feed **GRN inference**, while new quantitative metrics will be developed to measure GRN disorganization and **separate drift from breakdown**, enabling trajectory clustering and tipping-point prediction.

3) **International and/or industrial aspect(s):** The international component is **indispensable**: co-supervision with **Dr Norbert Perrimon (Harvard Medical School)** provides unique expertise in scalable functional genomics and GRN inference at scale. **Harvard will drive the network-reconstruction and modelling work, co-developing new disorganization metrics** and ensuring rigorous interpretation and global visibility.

5 keywords in line with EUR CARe

Aging heterogeneity, Frailty tipping points, Gene Regulatory Networks, system Modeling, Bioinformatic.

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

- **Pelletier A**, et al. Skelet Muscle. 2025. doi: 10.1186/s13395-025-00392-4.
- **Grangirard E**, et al. BiorXiv. 2025. doi: 10.1101/2025.10.08.681092
- **Labrosse M**, et al. BiorXiv. 2025. doi: 10.1101/2025.09.23.678035
- **Ahmad M**, et al. Nat Commun. 2025. doi: 10.1038/s41467-024-55371-y.
- **Droujinine IA**, et al. Nat Commun. 2021. doi: 10.1038/s41467-021-22599-x.