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MARK-AGE biomarkers of ageing

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ABSTRACT

Many candidate biomarkers of human ageing have been proposed in the scientific literature but in all cases their variability in cross-sectional studies is considerable, and therefore no single measurement has proven to serve a useful marker to determine, on its own, biological age. A plausible reason for this is the intrinsic multi-causal and multi-system nature of the ageing process. The recently completed MARK-AGE study was a large-scale integrated project supported by the European Commission. The major aim of this project was to conduct a population study comprising about 3200 subjects in order to identify a set of biomarkers of ageing which, as a combination of parameters with appropriate weighting, would measure biological age better than any marker in isolation.

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1. Introduction

Ageing has been defined as the time-dependent decline of functional capacity and stress resistance, associated with increased risk of morbidity and mortality. Ageing is a process that affects most if not all tissues and organs of the body. Moreover, cross-talk can occur between multiple physiological systems, *e.g.* metabolic systems may influence the ageing of the immune system. The mechanisms underlying the ageing process are beginning to be unravelled at the molecular level (López-Otín et al., 2013), yet there is clear evidence that the rate of ageing differs significantly between members of the same animal species, including humans. In other words, the "biological age" may differ from the chronological age.

The classical quantitative assessment of "the rate of ageing" relies on the analysis of mortality curves (Gompertz function) of populations. In other words, individuals have to be followed up until the end of their lives in order to determine their "biological age" at any time point during life. Therefore, at the level of a living individual, a reliable of assessment of the state of ageing, *i.e.* the state of the above-mentioned functional decline, and a prediction of the risk of the onset of morbidity and the residual individual life expectancy are not possible with this method.

One strategy to solve this problem is the identification of (an) age-related change(s) in body function or composition that could serve as a measure of "biological" age and predict the future onset of age-related diseases and/or residual lifetime more accurately than chronological age. Such parameters are termed "biomarkers of ageing" (Baker and Sprott, 1988). This term has been coined in analogy to biomarkers of specific chronic diseases, such as HIV infection, or biomarkers of exposure to toxins.

The American Federation for Aging Research has proposed the following criteria for a biomarker of ageing:

1. It must predict the rate of ageing. In other words, it would tell exactly where a person is in their total life span. It must be a better predictor of life span than chronological age.
2. It must monitor a basic process that underlies the ageing process, not the effects of disease.
3. It must be able to be tested repeatedly without harming the person, for example, a blood test or an imaging technique.
4. It must be something that works in humans and in laboratory animals, such as mice. This is so that it can be tested in lab animals before being validated in humans.

The fourth of the above criteria may, however, be questioned as there are certainly some parameters whose importance for the ageing process may differ between mammalian species. One example would be telomere shortening in humans and in laboratory mice: While in human somatic tissues telomere shortening can readily be detected, this is not the case in wild-type laboratory mouse strains owing to their much greater overall length of telomeres. Therefore eliminating some candidate parameters just based on their lack of relevance in some model systems may lead to an exclusion of parameters that are potentially interesting for the human system.

It should be noted that many candidate biomarkers of human ageing have been proposed in the scientific literature but in all cases their variability in cross-sectional studies is considerable, and therefore no single measurement has proven to serve a useful marker to determine, on its own, biological age. A plausible reason for this is the intrinsic multi-causal (Holliday, 2006) and multi-system nature of the ageing process. MARK-AGE was a large-scale integrated project supported by the European Commission. The major aim of this project was to conduct a population study comprising about 3200 subjects in order to identify a set of biomarkers of ageing which, as a combination of parameters with appropriate weighting, would measure biological age better than any marker in isolation.

2. MARK-AGE consortium

In order to tackle the scientific problem of establishing powerful biomarkers of human ageing, the MARK-AGE consortium, which consisted of 26 Partners comprising 21 non-profit organisations (universities and public research institutes), 3 small and medium sized enterprises (SMEs), and 2 large companies, was formed. The scientific groups involved are at the forefront in the field of ageing research, and some Partners are international leaders even in wider fields such as Genetics. The MARK-AGE consortium was characterised by a high degree of interdisciplinarity: The array of expertise ranged from Geriatrics, Epidemiology and Human Genetics to Clinical Chemistry, Biochemistry, Cell Biology, Immunology, Molecular Genetics, Bioinformatics and Mathematical Modelling. Such a level of interdisciplinarity is essential for the success of a project of this large scale. The lead researchers are the authors on this document.

3. The MARK-AGE strategy

In the Large-Scale Integrating Project MARK-AGE, the Partners proposed to perform a comprehensive and coherent Europe-wide population study aiming at the identification of powerful biomarkers of human ageing across a range of physiological

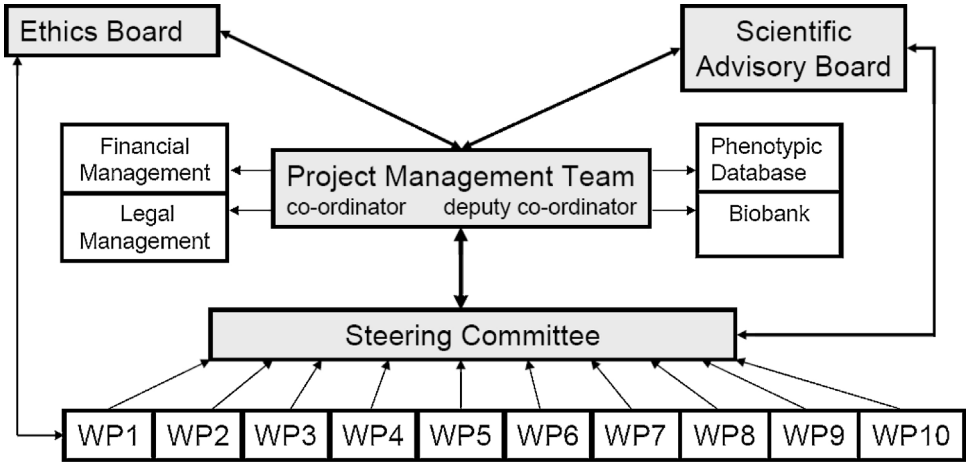

Fig. 1. Schematic representation of the management structure of the MARK-AGE project.

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