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MARK-AGE population: From the human model to new insights

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Many relevant EU projects were funded during last decade and MARK-AGE (European Study to Establish Biomarkers of Human Ageing) was the first focused on the identification of biomarkers connecting itself with a previous funded project, i.e. GEHA (Genetic of Helathy Ageing) that identified European families with longevity component (Franceschi et al., 2007). MARK-AGE was mainly a cross sectional study, based on definite assumptions, as it will be described below, and focused on an age range between 34 and 75 years, in order to identify early biomarkers of biological vs. chronological age, potentially capable of predicting the rate of ageing later in life. Complementarily, many anti-ageing strategies have been proposed, such as those related to immune system remodelling (Capri et al., 2006b), but a new era begun on different tissues-specific epigenomics (Horvath, 2013; Romanoski et al., 2015), food/nutrition science, diet intervention (Santoro et al., Q3 2014; Bacalini et al., 2014; Mercken et al., 2013; Cevenini et al., 2013; Berendsen et al., 2014) and its interaction with genomic background (Corella and Ordovás, 2014) and gut microbiota remodeling (Ottaviani et al., 2011; Biagi et al., 2013; Collino et al., 2013). These recent findings together with MARKAGE biomarkers not only give a new perspective in term of ageing rate measurement, but also new insights for molecular-targeted interventions to slow down human ageing process and likely, age-related pathologies onset.

Abbreviations: CS, Cockayne syndrome; DS, Down syndrome; GO, GEHA offspring; RASIG, randomly recruited age-stratified individuals from the general population; SGO, spouses of GO; WS, Werner syndrome.

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1. Ageing of European Countries

The proportion of elderly people over 65 years in Europe (EU-28Countries) is predicted to increase from 18.2% in 2013 to 28.7% by 2080 (Eurostat source). The share of those aged 80 years or above in the EU-28's population is projected to almost triple between 2013 and 2080. Thus, over the coming decades, Europe's demographic makeup will change harshly. Our populations are becoming older than ever before due to three major trends. First, the baby-boom generation approaches retirement age thus older people will rise rapidly; second, birth rates have remained low for several decades; and third, European people, but not only, are living longer lives, even if comorbidites and disabilities are increasing, especially after 62 years (Eurostat source). In 2011 the number of healthy life years at birth was estimated at around 62 years for men and 61 years for women in EU-28, meaning that approximately, 16% and 21% of unhealthy life for men and women, respectively, are expected. This demographic remodelling emphasises the critical importance of identifying new strategies able to counteract or slow down ageing and the onset of age-related diseases and disabilities. These new strategies can contribute to increase the number of elderly citizens in good health, and reducing age-related medical and social costs. Therefore the identification of biomarkers of healthy or unhealthy ageing (see Bürkle et al., this issue) and the adoption of healthy life styles before the use of drug-based therapies are necessary. This situation has pushed EU governance to identify scientific projects able to find solutions to monitor and counteract unhealthy ageing, thus promoting a healthy and active ageing.

2. From population to individual level

On the other side, the rate of ageing in humans is not uniform due to the complexity of genetics and epigenetics (Capri et al., 2006a, 2014), which interact with environment (Biagi et al., 2013; Garm et al., 2013) and stochasticity with diverse weights at different phases of life taking into account also embryonic and foetal development (Cevenini et al., 2010). Further, these main factors could differently affect the rate of ageing at the levels of cells, tissues or body systems within the same organism according to the hypothesis of the "mosaic of ageing" (Cevenini et al., 2008). Tissues and organs might age at different rate and further, individuals of same chronological age might have different biological age. This complexity makes more difficult the identification of a unique comprehensive mechanism of ageing and related biomarkers (Deelen et al., 2013).

3. The human model in MARK-AGE: innovative concepts

MARK-AGE aimed at the identification of biomarkers of ageing capable of distinguishing between chronological and biological ageing (see Giampieri et al., this issue) looking at systemic parameters assessed in the blood/urine and buccal mucosa cells (BMC) of volunteers, likely mirroring the entire organism. To achieve this objective a robust human model with definite assumptions was conceptualised accordingly (see Bürkle et al., this issue), as briefly described:

1. Subjects representing the "normal" aging: randomly recruited age-stratified individuals from the general population or RASIG, covering the age range 35–74 years;
2. Subjects representing the successful or "decelerate" aging: subjects born from a long-living parent belonging to a family with long living sibling(s) already recruited in the framework of the GEHA -Genetic of Healthy Ageing- project (Skytthe et al., 2011). These individuals ("GEHA offspring" or GO) were recruited together with their spouses or SGO representing the best control to evaluate possible life style effects, since they share the same environmental factors for many years with their partners.
3. Subjects representing accelerated aging: patients with progeroid syndromes (Cockayne, Werner and Down syndromes), characterised by accelerated "segmental" ageing, were recruited.

4. Independent variables in MARK-AGE

MARK-AGE model took into account essential independent variables, i.e. gender, age, geography. The selection of these variables was done on the basis of specific assumptions such as the major role of gender in the ageing process, the need to identify biomarkers before the late phase of life and the role of environment/geography/culture in the population ageing with a consistent number of individuals.

a GENDER. Males and females were recruited close to 50% in each age class, giving the possibility to analyse age-gender effects. Literature strongly suggests a gender effect on mortality rate. Females live longer even with a higher frequency of disabili-

Table 1
Strategies of MARKAGE dissemination applied by all the centres involved in the recruitment.

Centres	Population	Dissemination and strategy of recruitment
BioTeSys GmbH (DE)	RASIG	Newspaper articles, information evening at the town hall together with the governing mayor; registration office (letter/flyer), volunteers known from other trials conducted at BioTeSys a little word-of-mouth recommendation.
FUNDP/StratiCELL (BE)	RASIG/GO/SGO	Contacted an open-university for persons belonging to the 3rd age and all societal horizons; the Services of the Human Resources of the City of Namur, the Univ. of Namur, Univ. Clinics of Mont-Godinne, and Regional Hospital Centre, dealing with all sorts of personnel; organised press conference at Univ. of Namur (many press articles, interviews on national radios, local TV news, national TV programme on ageing). GEHA reference for GO list
LUMC (NL)	GO/SGO	Drafted a list with a number of picked nominatives (GEHA reference).
NHRF (GR)	RASIG/GO/SGO	Contact by email all the personnel of Research Institutes of Athens. i. Contact by phone, call all the GEHA siblings giving information to GO/SGO on MARK-AGE, sending them the informative sheet by post or fax. ii. Contact by phone, call all our personal acquaintances giving information on MARK-AGE
NENCKI (PL)	RASIG/GO/SGO	Obtained addresses of 3200 RASIG from Ministry of Interior and Administration (presently Ministry of Interior) according to PESEL (National Electronic Census Number System); sent 1700 letters of invitation, the responders feedback by phone or e-mail (22%). GEHA reference for GO list.
UIBK (AT)	RASIG	Articles in a very common Tyrolean daily newspaper; dissemination on local TV news and articles in other newspapers and magazines.
UNIBO (IT)	RASIG/GO/SGO/DS	GO/SGO were recruited before RASIG: drafted a list with a number of picked nominatives. RASIG: population of PIANORO (17,000 inhabitants) near Bologna; contacts with the Mayor Citizen and the District of Public Health. A presentation of the project was performed to all the population with local Government and general practitioners; local paper, information flyers; magazine associated to food discounts) and TV, recruited also persons from the University of Bologna. DS and their family were contacted by specific association in Bologna
UTA (FL)	RASIG/GO/SGO	Newspapers, local TV announcements

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