

FUTURAGE:
A Road Map for Ageing Research
- Biogerontology

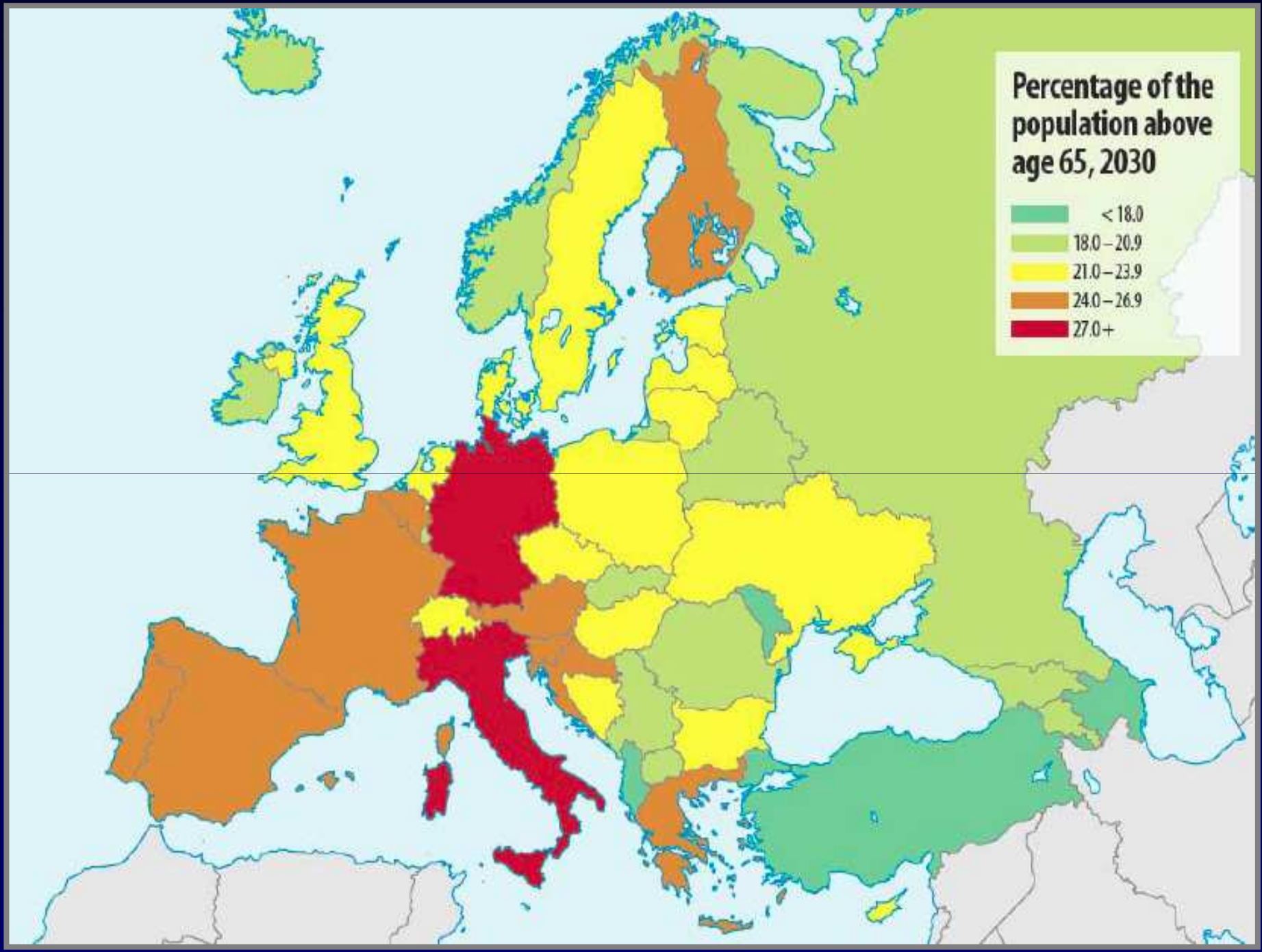
Dr Stathis Gonos

* Director of Research, National Hellenic Research Foundation

* Executive Committee Member, International Union of Biochemistry &
Molecular Biology

Percentage of the population above age 65, 2030

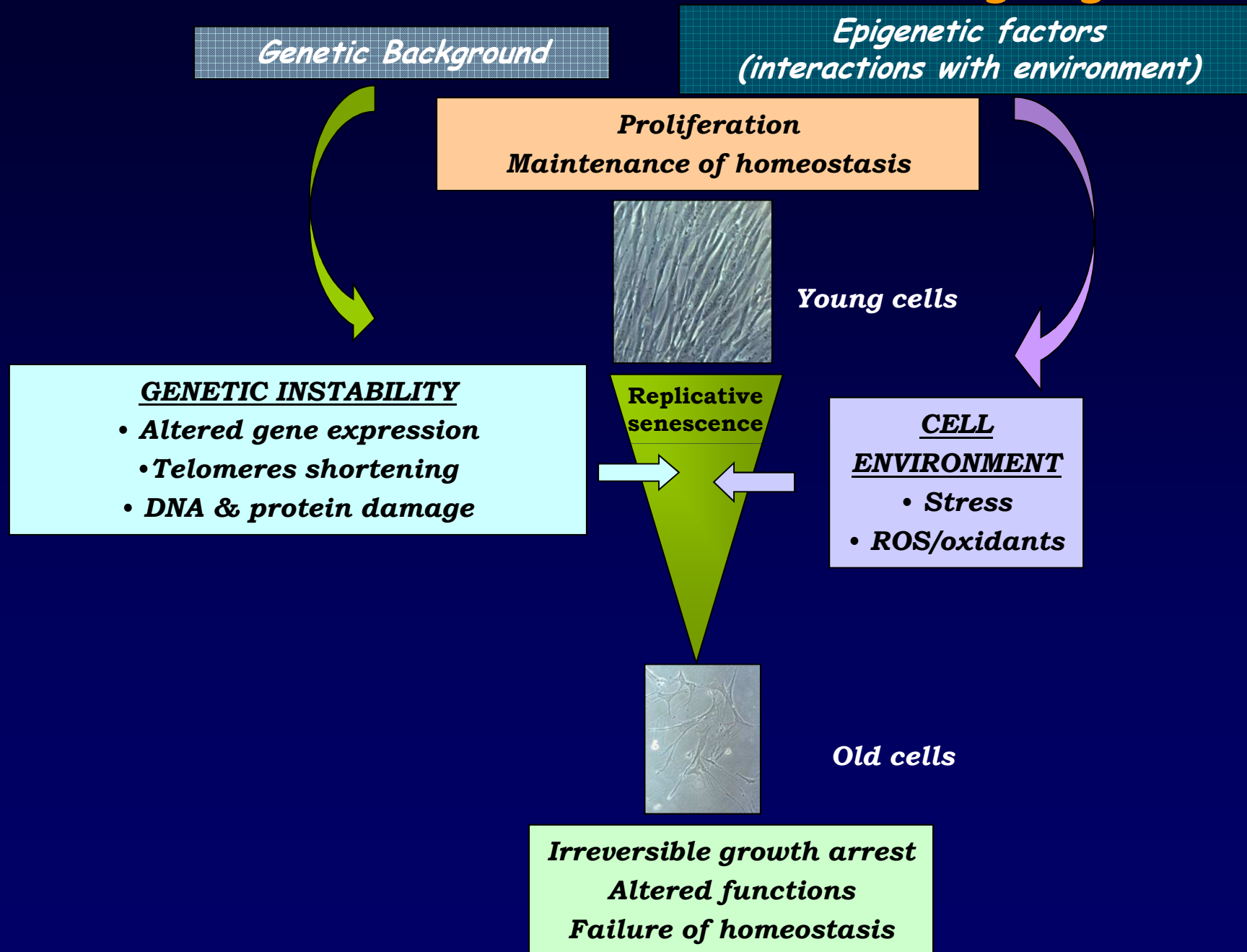
- < 18.0
- 18.0 - 20.9
- 21.0 - 23.9
- 24.0 - 26.9
- 27.0+



Biogerontology:

**understanding the biological causes of
human ageing and longevity**

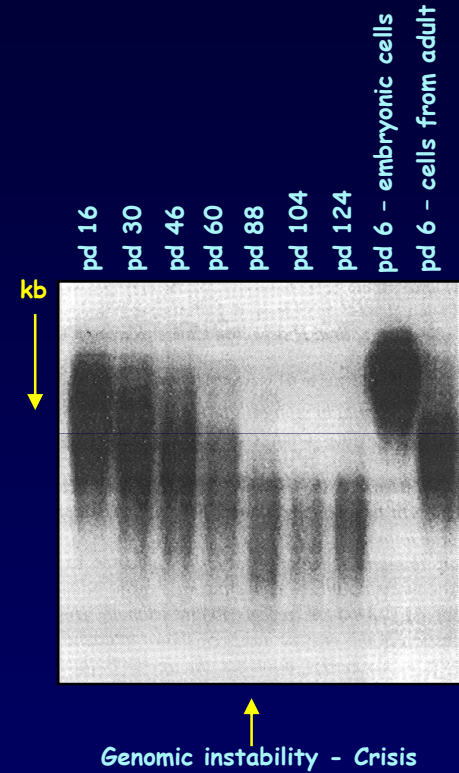
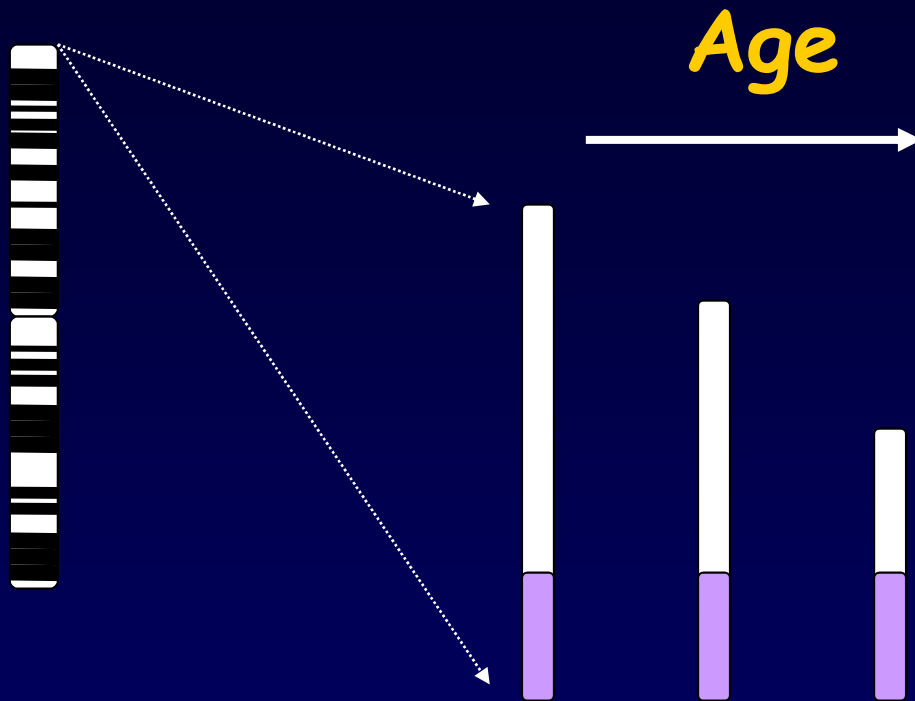
Factors that influence human ageing



Is it a biological clock?

The discovery of telomeres

Nobel prize, 2009



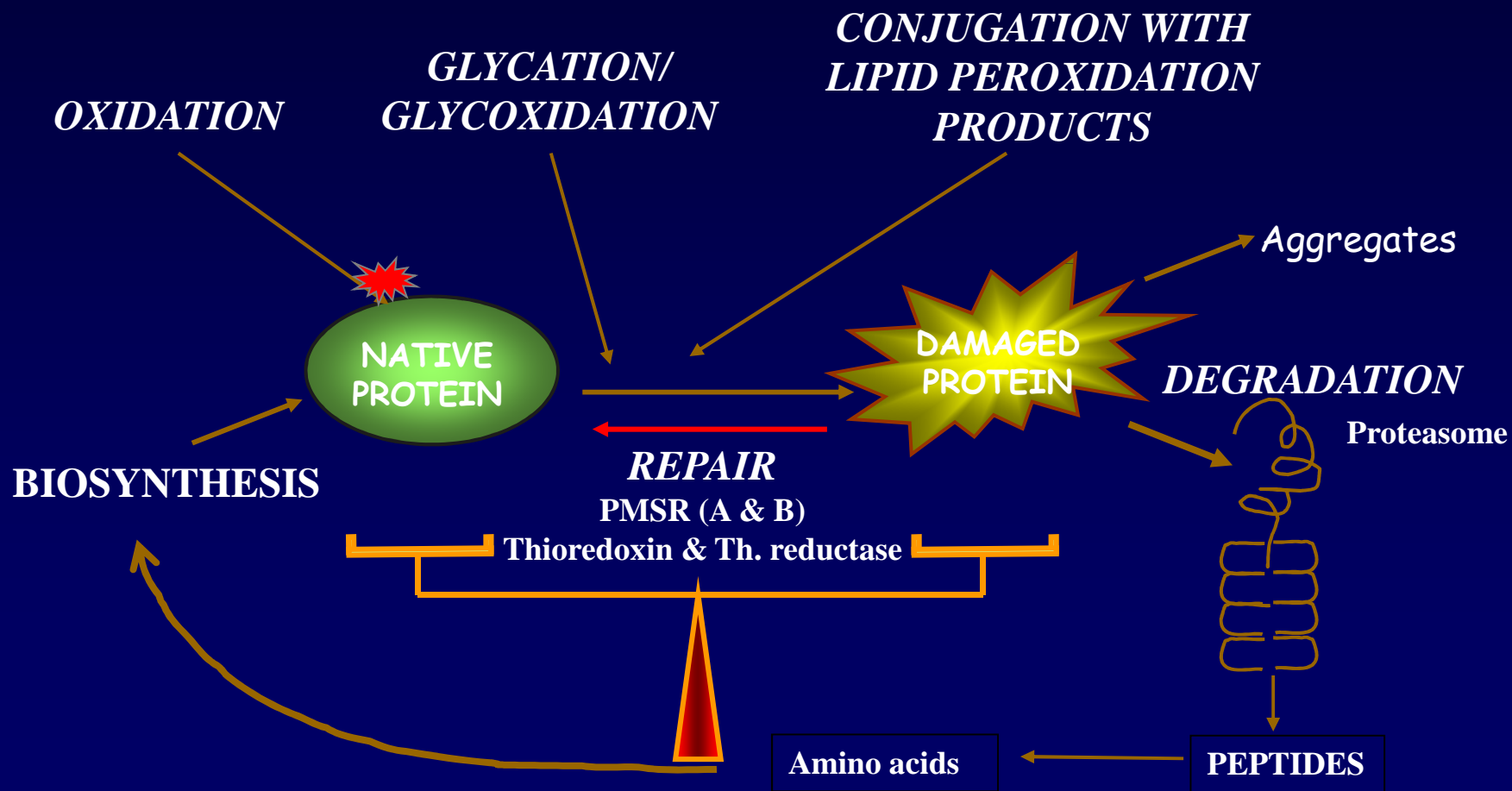
Telomeres: (TTAGGG)_n
Human somatic cells:
Loss of ~100bp/cell division

Ageing associates with accumulation of damage

The discovery of the major cellular
proteolytic machinery

Nobel prize, 2004

Protein maintenance systems in oxidative stress and ageing



**Proteasome “activation”
significantly delays ageing**

List of the projects financed under the 6th and 7th Framework Programmes of the European Commission

- * **GEHA** - Coordinator Claudio Franceschi - <http://www.geha.unibo.it>
- * **MIMAGE** - Coordinator Heinz Osiewacz – <http://www.mimage.uni-frankfurt.de>
- * **PROTEOMAGE** - Coordinator Brian Clark – <http://www.proteomage.eu>
- * **CRESCENDO** - Coordinator Barbara Demeneix – <http://www.crescendoip.org>
- * **ELASTAGE** - Coordinator Pascal Sommer - <http://www.elastage.org>
- * **LIFESPAN** - Coordinator Rudi Westendorp – <http://www.lifespannetwork.nl>
- * **MARK-AGE** - Coordinator Alexander Burkle – <http://www.mark-age.eu>
- * **TOLERAGE** - Coordinator Georg Wick - <http://www.cemit.at/tolerage>
- * **MYO-AGE** - Coordinator Gillian Butler-Browne – <http://ns356946.ovh.net/-myoage>
- * **RESOLVE** - Coordinator Lutz-Henning Block – <http://resolve.punkt-international.eu>

The genetics of healthy ageing in Europe

- ❖ Recruitment of 90+ years old siblings (i.e. 0.5% of the longest lived population in Europe) and younger controls from 12 European countries & China
- ❖ Perform a genome scan in order to identify candidate longevity genes

Biobank:

<i>Families with two siblings:</i>	<i>2,347</i>
<i>Families with three siblings:</i>	<i>195</i>
<i>Families with four siblings:</i>	<i>22</i>
<i>Families with five siblings:</i>	<i>4</i>
	<i>5,390 (total samples)</i>
<i>Controls (spouses of their children):</i>	<i>2,493</i>

Genetic Data

Peak	chr14	chr17	chr19p	chr19q	chr19q-fem females	chr17 weighted with age
Centre	(0-12)	(68-88)	(20-42)	(58-72)	(74-90)	(70-90)
Odense	1.38	1.03	1.98	2.36	1.90	0.88
Belfast+Newcastle	0.11	<p style="color: red; text-align: center;">There are about 1000 genes that would be of interest because they are in the 1-LOD-drop area beneath each linkage peak.</p> <p>1) Chr 14: 0-12 cM => 19.6 – 22.8 Mb, 78 genes 2) Chr 17: 68-88 cM => 34.1 – 52.9 Mb, 331 genes 3) Chr 19p: 20-42 cM => 7.0 – 17.3 Mb, 281 genes 4) Chr 19q: 58-72 cM => 39.4 – 51.4 Mb, 337 genes</p>				
Newcastle	0.01					
Leiden	1.98					
Montpellier	0.95					
Greece	1.10					
Bologna	0.21					
Rome+Bologna	0.36					
Calabria	-0.01	0.96	0.76	0.75	0.56	0.91
Sassari	0.28	0.45	0.04	0.01	0.03	0.42
Kiel	-0.01	0.11	0.95	0.26	-0.05	0.21
Varsova	0.091	0	0.06	0.04	1.11	----
Louvain	0.01	0.41	0.41	0.21	0.01	-----
Kiev	0.29	0.34	0.47	0.67	1.41	-----
Tampere	0.68	1.75	0.4	0.18	0	1.47

A panel of 6090 highly polymorphic SNPs evenly distributed over the entire genome was used to test whether affected siblings (affected by longevity) share more alleles identical by descent (transmitted to them from the same parent) than expected by chance. **A linkage signal above 0.9 is considered significant.**



“MARK-AGE”

European Study to Establish Biomarkers of Human Ageing
(HEALTH-F4-2008-200880; <http://www.mark-age.eu/>)

April 2008 - March 2013



Population Study (~3,700 volunteers)

(1) “**RASIG**” (randomly recruited age-stratified individuals from the general population covering the age range 35-74 years. ~**2,400 volunteers**)

(2) “**GO**” + “**SGO**” (**GEHA** Offspring + Spouses of **GEHA** Offspring). ~**700 + 600 volunteers**)

(3) A small number of patients with **progeroid syndromes** (CS: **Cockayne's Syndrome** patients, DS: **Down's Syndrome** patients, WS: **Werner's Syndrome** patients).

Parameters will be studied..

- **“Classical” physiological parameters:**
 1. Body mass index
 2. Waist and hip circumference
 3. Blood pressure at rest
 4. Heart rate at rest
 5. Lung capacity- FEV1
 6. Lung capacity- FVC (forced expiratory vital capacity)
 7. Near vision
 8. Five-times chair standing
 9. Handgrip strength
- **Clinical chemistry analyses:**
 10. Blood urea nitrogen and creatinine
 11. Fasting glucose and fasting insulin
 12. Glycosylated hemoglobin (A1C)
 13. Albumin and serum protein concentration
 14. Fasting triglycerides and free fatty acids
 15. Total cholesterol, HDL and LDL-cholesterol
 16. Noradrenalin, serotonin and 17-hydroxycorticosteroid
 17. C-reactive protein (CRP) and fibrinogen
 18. Serum amyloid A and P, and pentraxin 3
 19. Adiponectin
 20. Testosterone (will be measured in males only)
 21. Prostate specific antigen (PSA)

Parameters will be studied..

- **Specialised tests established by Partners:**
 22. Cellular poly(ADP-ribosyl)ation capacity and DNA repair in PBMC
 23. DNA methylation status in PBMC
 24. Telomere length in PBMC
 25. Changes in mitochondrial DNA in blood cells
 26. *APOE* genotype
 27. Vitamin levels in mucosal cells
 28. Zn, Cu, Se and Fe in plasma and PBMC; metallothionein expression
 29. Oxidative stress markers
 30. Glycation
 31. Serum glycans
 32. Cytokines
 33. ApoJ/clusterin
 34. Proteasome, methionine sulfoxide reductases
 35. Immunity against specific pathogens
 36. Autoantibodies
 37. Damage-Induced Cell Death and Activation-induced cell death in lymphocytes
 38. Thymic output
 39. Serum lipids including LDL particle size
 40. Isoprostanes
- **Novel biomarkers yet to be established:**
 41. Serum and PBMC proteomics
 42. Metabonomics
 43. Gene expression and protein profiling of blood cells (B cells, T cells) exposed to physiological oxygen tension
 44. Proteins secreted by endothelial cells and fibroblasts
 45. Biomarkers of ageing in the mouse and in Cockayne's syndrome patients
 46. microRNAs

QuickTime™ et un
décompresseur TIFF (non compressé)
sont requis pour visionner cette image.



Coordination & Consolidation of European Biogerontology

Link-Age

14 members & > 50 associate members

<http://www.link-age.eu/>

Coordinator : O. Toussaint



A road map for European research on molecular aspects of healthy ageing

“WhyWeAge”

Coordinator: Dr Olivier Toussaint

- **What are the current & potential themes of research in the field?**
- **What is the current & potential work force in the field in Europe?**
- **How to develop further the current functional networks?**
- **What is the knowledge on biological ageing in each of the topics?**
- **What is the state of the art as for the interactions between medicine, biology & social sciences?**
- **How to ameliorate (interdisciplinary) collaborations?**
- **What axes of research (and why) need to be developed in the next 10-15 years in Europe?**
- **What are the priorities considering the different stakeholders?**
- **Who will be the recipients of the progress made considering the different stakeholders (from scientists to socio-economic benefits)?**

The 12 thematic workshops:

- 1. Biomarkers of ageing and longevity. Alexander Bürkle and Stathis Gonos**
- 2. Vascular ageing. Jorge Erusalimsky**
- 3. Mitochondria and senescence. Pidder Jansen-Dürr, Claudio Franceschi and Thomas von Zglinicki**
- 4. Oxidative stress, protein damage and protein maintenance. Bertrand Friguet, Grzegorz Bartosz and Csaba Soti**
- 5. Telomeres and DNA damage. Alexander Bürkle and Thomas von Zglinicki**
- 6. Immunosenescence and inflammation. Graham Pawelec and Claudio Franceschi**
- 7. Metabolism. Hilde Nebb and Barbara Demeneix**
- 8. Sarcopenia, muscle weakness and physical exercises. Gillian Butler-Browne**
- 9. Skin ageing and elastic tissues. Pascal Sommer, Michel Salmon and Christos Zouboulis**
- 10. Nuclear receptors and Systems Biology. Barbara Demeneix and Daryl Shanley**
- 11. Biotechnologies in Biogerontology. Olivier Toussaint, Michel Salmon and Brian Clark**
- 12. Clinical Biogerontological studies. Christian Swine and Christos Zouboulis**



“WhyWeAge”

Summit:

Brussels, May 17th-19th, 2010