



Immunosenescence and Its Applications to Artificial Immune Systems

Graziela Figueredo

gzf@nott.ac.uk

Room B36

Supervisors:

Prof Uwe Aickelin

Dr Amanda Whitbrook



Overview

- Aging
- Immunosenescence
- Causes
- Factors Associated
- Models
- Proposed Model
- Other Applications
- Conclusions and Future Work

Aging

Endocrine
Function

Brain
Function

Cardiovas-
cular
Health

IMMUNOSENESCENCE

Glucose
Disregulation

Muscles
and Bones
problems

Oxidative
Stress



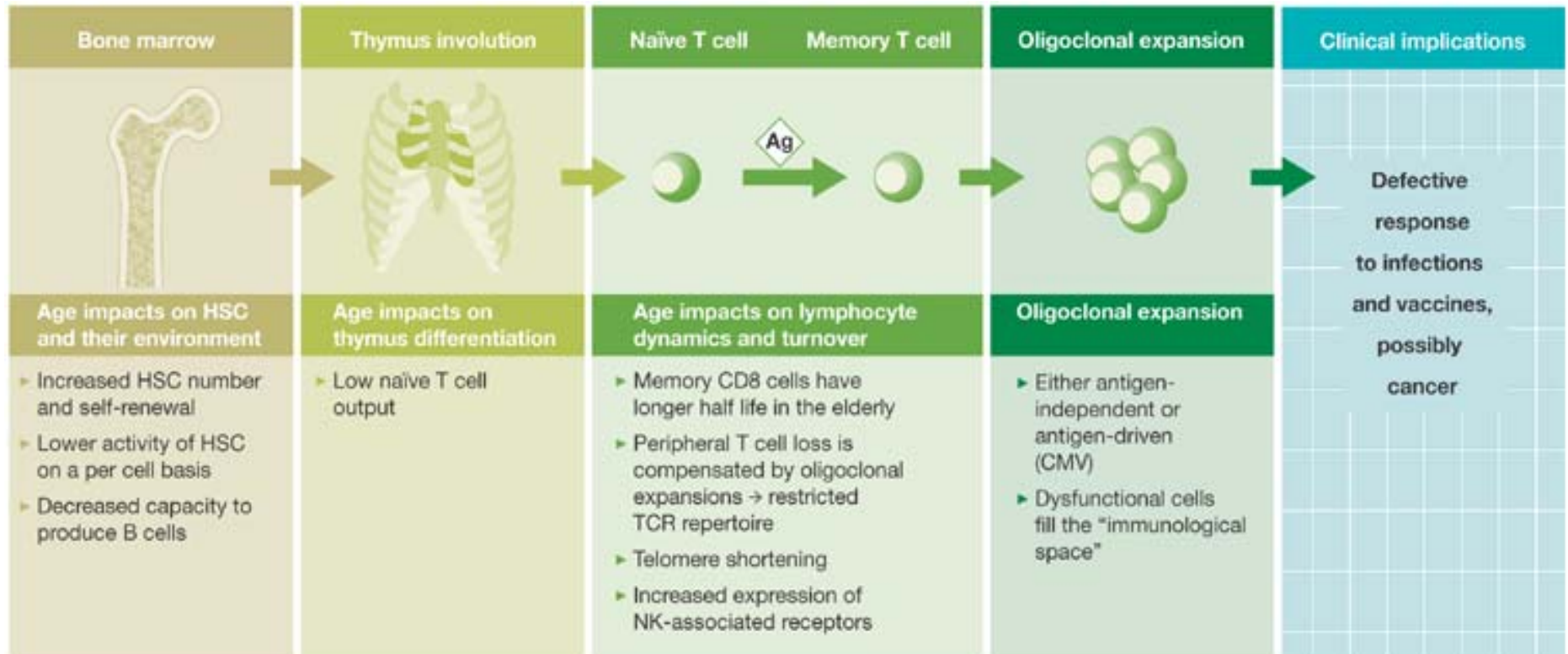
Immunosenescence

- Progressive changes in the IS that decreases the individual's capacity to produce effective immune responses
- Decay of immunocompetence in the elderly
- Loss of functionality

Immunosenescence – some causes

- Lifelong antigenic stress
- Filling of the immunological space
- Accumulation of effector T and memory cells
- Reduction of naïve T cells
- Deterioration of clonotypical immunity
- Up-regulation of the innate IS







Immunosenescence – some factors associated

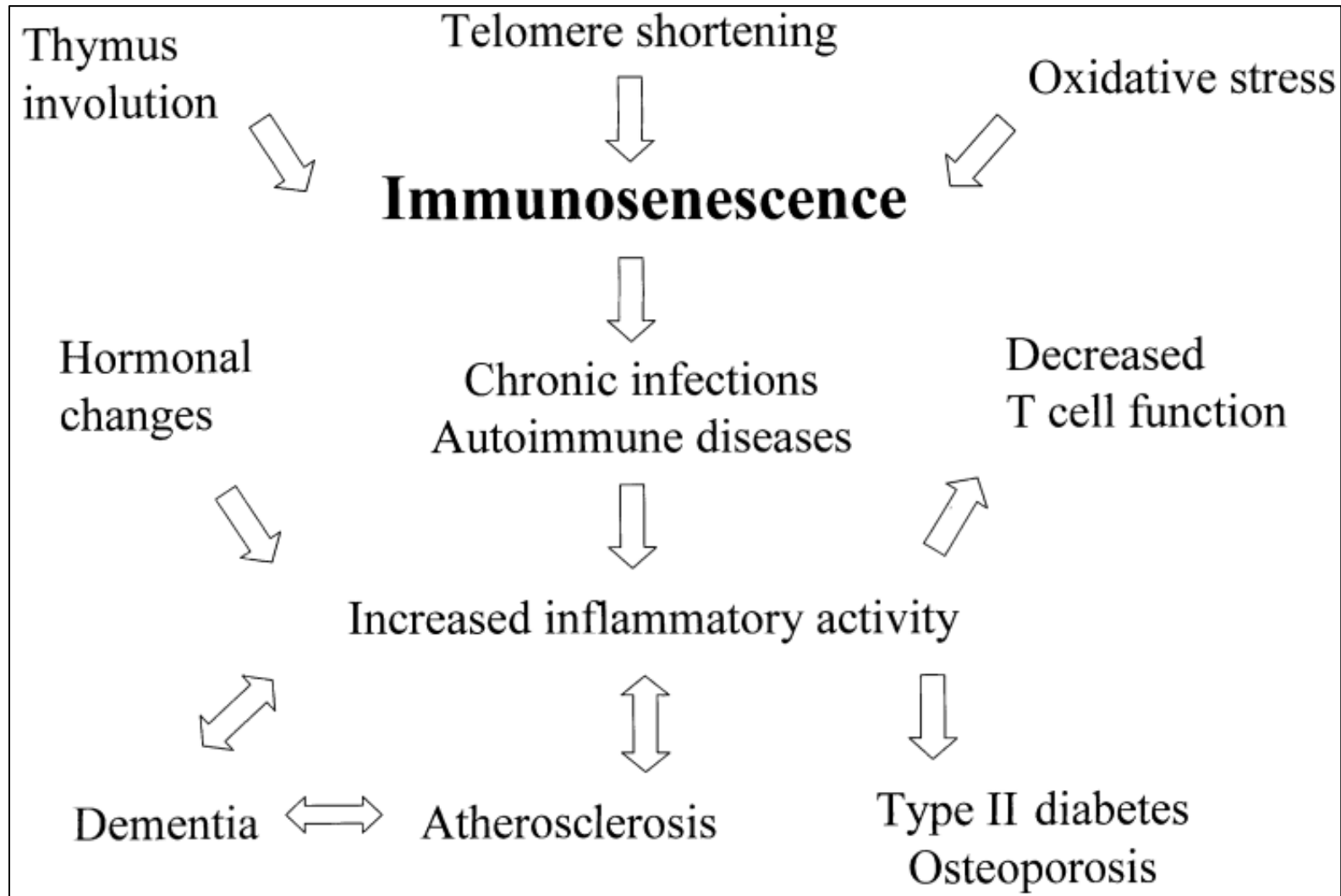
- Mitochondrial damage causing tissues disfunction
- Micronutrient inadequacy accelerates aging because of metabolic malfunctioning
- The number of telomeres is proportional to life expectancy. They avoid DNA damage
- DCs reactivity to self antigens – risk of triggering autoimmune diseases



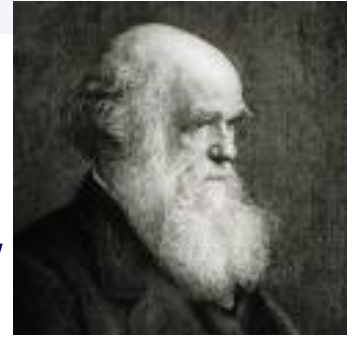
Immunosenescence – some factors associated

- Decrease in responsiveness to vaccination
- CMV seropositivity
- Increase of autoantibody frequency
- Reactive oxygen species (ROS) causes damages to cellular components over time
- Chronic inflammation
- Reduced capacity to recover from stress-induced modifications

Immunosenescence - facts



Immunosenescence – from the evolutionary point of view



- Subject to evolutionary constraints
- Humans lived 30-50 years a couple of centuries ago. Nowadays, 80-120. This is longer than predicted
- Antigenic burden encompassing decades of evolutionary unpredicted exposure
- The evolutionary recent defence mechanisms deteriorate with age
- Old and gross mechanisms are preserved/up-regulated



Immunosenescence – from the evolutionary point of view

- Antagonistic pleiotropy: natural selection has favoured genes conferring short-term benefits at the cost of deterioration in later life
- IS has probably been selected to serve individuals only until reproduction
- After that, biochemical processes proceed freely without past selective pressure to improve the life of an individual
- Thymic involution in early age supports these hypothesis



Immunosenescence – candidates for computational simulation models

- Space Filling

- Shrinkage of naïve T cells repertoire
- Increase of memory
- Loss of T cell diversity
- Accumulation of clones of restricted types



Immunosenescence – candidates for computational simulation models

- Lack of Naïve T Cells
 - Involution of thymus
 - Decrease of new phenotypic T cells output
 - T cells produced by peripheral expansion
 - Filling of the immunological space with copies of existing T cells
 - Possibility of memory T cells reversing back to naïve



Immunosenescence – candidates for computational simulation models

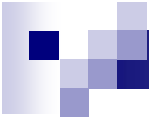
- Innate up-regulation
 - Decay in functioning of main phagocytes (macrophages, neutrophils and DCs)
 - Deregulated immune and inflammatory responses
 - Suppression of T cell functioning



Immunosenescence – candidates for computational simulation models

■ Accumulation of Treg Cells

- The amount of regulation has influence on the effectiveness of the immune response
- Accumulation or reduction of Treg cells inhibits or prevents some immune responses
- Higher risk of immune mediated diseases, cancer and infections



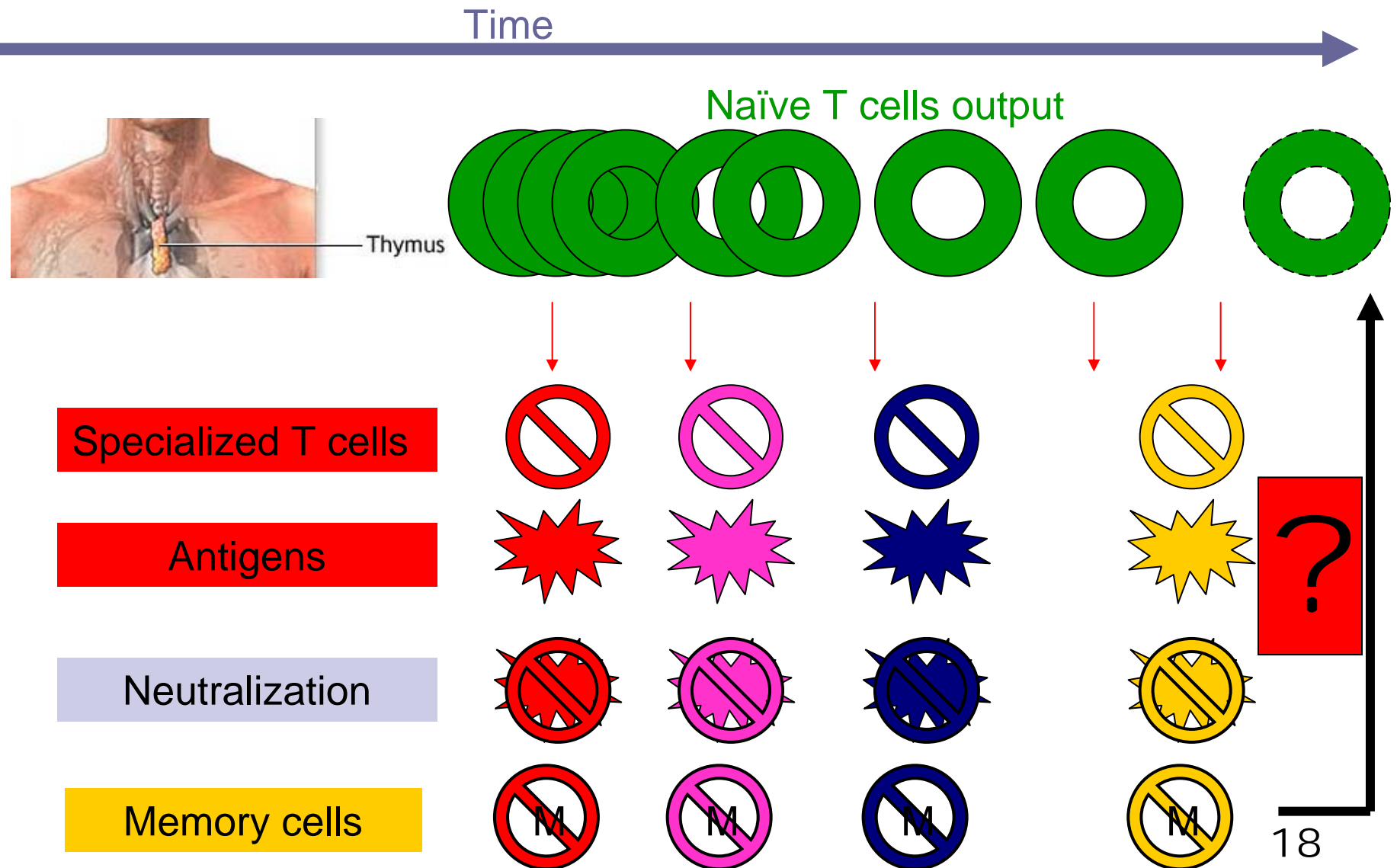
Theories				
Characteristics	<i>Space Filling</i>	<i>Lack of Naive</i>	<i>Innate up-reg</i>	<i>Treg Acum.</i>
Shrinkage of naïve cells	☑	☑		
Decrease of diversity	☑	☑		
Few clone types taking space	☑	☑		
Excessive memory cells	☑			
Loss of clones		☑	☑	☑
Inflammation			☑	☑
Excessive T cell suppression			☑	☑
Degeneration	☑	☑	☑	☑
Auto-immunity	☑	☑	☑	☑
Decrease in vaccine response	☑	☑		☑




Immunosenescence – one first model

- Decrease of thymic output
- Lack of naïve T cells
- Peripheral expansion
- Antigenic stress
- Space filling
- How would the system behave if memory could turn back into naïve?


First model - schematically






Immunosenescence – other computational applications

- Other simulation models to investigate how the process of immunosenescence
 - Take place
 - Develop
 - Propagate
 - Evolve
 - Turn out to be destructive
 - Could be slowed down



Immunosenescence – other computational applications

- Analysis of immunosenescence related datasets in order to
 - Find out association rules
 - Investigate how micronutrients and antioxidants could slow down degeneration
 - Prediction of vaccination effectiveness in a certain individual



Immunosenescence – other computational applications

- Detection/prediction of aging/degeneration in
 - Control systems
 - Software
 - Social Networks



Degenerative Systems

- Those that, through a series of sequential events devolves in time until functionality is compromised.
 - Examples:
 - Safety and security
 - Water distribution
 - Transport
 - Energy
 - Product Quality
 - Computer Network
 - Social Network
 - Control



Software Aging

- SWs have a life cycle that suffer:
 - changes on the environment over time
 - loss of resources for a good functioning

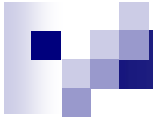
- From the HW:
 - Performance degradation (memory, processing time, fragmentation, errors)

- From the SW:
 - New demands and requisites
 - Errors introduced in new versions
 - Keeping competitiveness



Final Considerations

- Immunosenescence
- Computational modelling
- Detection of age parameters
- Other applications as future work



Questions?





Bibliography

1. Johnson, T.L.: Degenerative systems. In: Proceedings of the 42nd IEEE Conference on Decision and Control, IEEE (2003) 5135-5136
2. Bulatti, M., Pellican, M., Vasto, S., Colonna-Romano, G.: Understanding ageing: Biomedical and bioengineering approaches, the immunologic view. *Immunity & Ageing* 5 (2008)
3. Franceschi, C., Bonaf, M., Valensin, S.: Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the crowding of immunological space. *Vaccine* 18 (2000) 1717-1720
4. Martinis, M.D., Franceschi, C., Monti, D., Ginaldi, L.: Inflamm-aging and lifelong antigenic load as major determinants of ageing rate and longevity. *FEBS* 579 (2005) 2035-2039
5. Eric Boren, M.E.G.: Inflamm-aging: autoimmunity, and the immune-risk phenotype. *Autoimmunity reviews* 3 (2004) 401-406
6. Candore, G., Colonna-Romano, G., Balistreri, C.R., Carlo, D.D., Grimaldi, M.P., List, F., Nuzzo, D., Vasto, S., Lio, D., Caruso, C.: Biology of longevity: Role of the innate immune system. *Rejuvenation Research* 9 (2006) 143-148.
7. Murray, J.M., Kaufmann, G.R., Hodgkin, P.D., Lewin, S.R., Kelleher, A.D., Davenport, M.P., Zaunders, J.: Naive T cells are maintained by thymic output in early ages but by proliferation without phenotypic change after twenty. *Immunology and Cell Biology* (2003) 487-495
8. Wenisch, C., Patruta, S., Daxbrock, F., Krause, R., Horl, R.: Effect of age on human neutrophil function. *J. Leuk. Biol.* 67 (2000) 40-45
9. Butcher, S., Chahel, H., Lord, J.M.: Ageing and the neutrophil: no appetite for killing? *Immunology* 100 (2000) 411-416
10. Agrawal, A., Agrawal, S., Tay, J., Gupta, S.: Biology of dendritic cells in aging. *JCI in Immunol* 28 (2007) 14-20



Bibliography

11. Wu, D., Meydani, S.N.: Mechanism of age-associated up-regulation in macrophage pge2 synthesis. *Brain, Behavior, and Immunity* 18 (2004) 487-494
12. Sharma, S., Dominguez, A.L., Lustgarten, J.: High accumulation of t regulatory cells prevents the activation of immune responses in aged animals. *The Journal of Immunology* 177 (2006) 8348-8355
13. Colonna-Romano, G., Bulati, M., Aquino, A., Vitello, S., Lio, D., Candore, G., Caruso, C.: B cell immunosenescence in the elderly and in centenarians. *Rejuvenation Research* 11 (2008) 433-439
14. Parnas, D.L.: Software aging. In: *ICSE '94: Proceedings of the 16th international conference on Software engineering*, Los Alamitos, CA, USA, IEEE Computer Society Press (1994) 279-287
15. Grottke, M., Trivedi, K.S.: Fighting bugs: Remove, retry, replicate, and rejuvenate. *Computer* 40 (2007) 107-109
16. Janeway, C.A., Travers, P., Walport, M., Shlomchik, M.: *Immunobiology : the immune system in health and disease*. 5 edn. Garland Pub. (2001)