

## SYSBIOMED Workshop on 'The Ageing-Cancer Link' and Systems Biology

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### Participants

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Ageing is not a disease. However, many serious disorders are obviously correlated with age, their incidences often being significantly higher in the elderly population. Epidemiological data suggest that the incidence of certain cancers, such as colorectal carcinoma (CRC) and prostate cancer, is age-dependent. A large variety of mechanisms, ranging from accumulated damage by radiation, oxidative stress, infections, etc., to dysfunctional DNA repair, that might underlie the links between cancer and ageing are currently under **debate**. Looking closer, one needs to distinguish three groups of cancers: tumour diseases correlated with genetic predisposition (e.g. breast cancer); cancers with likely involvement of stem cells (e.g. testicular cancers); and typical childhood cancers (e.g. some **leukemias**). Failed tumour suppression, an impaired immune system and accumulated damage are considered responsible for the emergence of age-related **cancers**; tumour suppressor proteins, ageing genes and environmental stress representing the obvious links to ageing-related processes.

The participants agreed that causal mechanisms of ageing and the interplay of putative key factors are not well known today. Many different processes seem to be involved. For

example, cellular senescence, i.e. the loss of the ability to divide after a certain number of cell divisions, is considered a major cause since it limits the potential of tissue regeneration. The role of stem cells is a major challenge to both ageing and cancer research. Another puzzle to be solved is the role of sirtuins, NAD-dependent histone deacetylases, found in both prokaryotes and eukaryotes. They affect cellular metabolism through selective gene expression in eukaryotes and may be able to control age-related disorders like obesity, metabolic syndrome, type II diabetes mellitus and Parkinson's disease. Comparing fruit flies which live a few days, birds species that live up to seven decades and plants that enjoy lifespans of several centuries, one finds that cell differentiation is obviously decisive: the arrested growth of the somatic cells of fruit flies is responsible for accumulating eventually lethal damage. Regeneration and maintenance of cells is essential for birds which have low reproductive rates and need to mobilise energy reserves for long-distance migration. The longevity of plants is essentially due to the ability of plant cells to reverse differentiation when regenerating tissues. Moreover, caloric restriction is generally believed to extend the life-span of many organisms. Intensive research efforts will have to be devoted to the striking difference of the susceptibilities of different organs to tumour formation (e.g. heart vs. breast tissue). A review by Toren Finkel *et al.* gives a comprehensive summary of the current knowledge of the ageing-cancer link.<sup>1</sup>

### **Integrative approaches**

The participants are well aware of the many research projects on ageing currently funded in EC framework programmes (e.g. AGEACTION "Changing Expectations of Life" within FP6). Systems biology approaches are expected to complement these efforts and to provide deeper insights into some specific questions, such as those addressed by the following research proposals collected from the participants:

- Investigate the possible feedback loops between sirtuins and p53 by monitoring the response, in terms of tumour incidence and ageing symptoms, to sirtuin activators and inhibitors. **Suitable animal models include** mice, short-lived fish (Notochorda) and cell cultures expressing fluorescently labeled proteins that make it possible to study the proteins' dynamic behaviour. Ultimate aim: identify (combinations of) agents capable of preventing or curing cancer without causing premature ageing.

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<sup>1</sup> *The common biology of cancer and ageing*, Toren Finkel, Manuel Serrano, Maria A. Blasco, Nature 448, 767-774 (2007)

- *Individual level*: Study differences in nutrition, nutrition history and body size related to tumour **growth** by a model consisting of a hierarchy of allocation rules (modification/extension of the  $\kappa$ -rule in dynamic energy budget theory, DEB). *Cellular level*: Study and simulate population dynamics of mitochondria affected by ROS (reactive oxygen species), using data from unaffected, healthy mitochondria populations monitored under different nutritional conditions. *Ecological level*: Compare ageing in different species with respect to timing of reproduction; how is ageing connected with the genetic diversity of germ cells? (modelling context: body size scaling in DEB theory). Technologies to precisely monitor tumour growth in a non-invasive manner and quantitative biochemical indicators of ROS damage are required.

- Large scale effort to identify targets that are responsible for prolonging the *health-span* of humans. Ideal animal model system would be primates, better humans, other: mice and dogs. Data sources: SNPs, micro arrays, metabolome, proteome profiling, topome data.

*Structures*:

European Ageing Research Laboratories (EARL) that spend a third of their funds to external labs (collaboration grants) with a minimum bureaucratic burden.

- Discriminate between those causes of cancer that are genuinely related to the ageing process and those that depend on *time* rather than *age* (e.g. the onset time of virus-related tumours depends on the incubation time rather than on the host's age *per se*). *In silico* multiscale mathematical models are pointless if not combined with 'wet' experiments.

- Are ageing cells (suboptimal functions, mutations etc.) more prone to develop cancer? Studying transformed epithelial cells and the emergence of cancerous stroma cells: Is the aberrant stroma often observed surrounding tumours a cause or a consequence of the malignancies? (Special project: What is the role of the ubiquitin ligase encoded by BRCA1 which affects multiple important players like cell cycle (CC) proteins and the estrogen signalling pathway?)

Approach: Prospective population studies on breast cancer in age groups 30-40 and 60-70.

Comparison of premalignant and healthy tissue in non-tumour environment with early tumour and later stage tumour tissues by studying stroma in healthy tissue, tissue with early-stage tumour and tissue with advanced tumour. Methods: Comparative genome hybridisation

(CGH) studies, cytogenetic analysis, and monitoring how the level of genetic instability and length of the telomeres evolve in time course.

Consortium funded by EC: Collection of tissue samples (Austria, France), CGH (London, Sanger Institute), Cytogenetics (Athens), Arrays (Geneva, Lausanne), telomere analysis (indirect immunofluorescence lab, Athens)

- Is the observed correlation between diet and cancer/ageing due to a causal relation? *Related to ageing*: Study DNA metabolism in very long-lived, slowly evolving animals (bird species, salamanders, lampshells, chelonians). Systems: cell cultures. Methodologies: metabolic analysis, cell cycle analysis. Collaboration with relevant countries, such as the Seychelles. *Related to cancer-ageing link*: Effects of fruit/ fresh vegetables on genomic stability? Systems: Cultures of human cells, biopsies. Methodologies: analysis of gene-specific repair replication, expression, mismatch correction, and methylation. Analysis of protein methylation as function of supplementation; bioinformatics is needed, and systems biology is essential for interpretation of results.

- What is the role of cellular senescence in ageing and is there a link to between ageing and cancer? *Systems*: human fibroblasts, gut epithelium, stem cells. *Methodologies*: micro array analysis, proteomics. Modelling attempts would need to include information on oxidative stress, mitochondrial telomeres, DNA damage vs. repair, signalling pathways (p53, p21 etc.).

- How do cells decide between senescence, proliferation, apoptosis? Is ageing reversible? The answers should shed light on the development of processes leading eventually to tumour formation and/or ageing. Experimental systems should be as close as possible to humans.

Generally, it was felt that modeling should be done on various levels (cells, organs, organism) independently and that the models should then be integrated at a later stage. Comments were made that the data situation with respect to the ageing-cancer problem is difficult since patient data is available but data is rarely available from the "pre-cancer" phase.