HUMAN LIFE EXTENSION
PROGRAM
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APPROACHES TO STUDYING AGING PROCESS AND THEIR USE IN THE COMPLEX INTER-DISCIPLINARY 'HUMAN LIFE EXTENSION' PROGRAM

WE OPINE THAT EXTENDING HUMAN lifespan and particularly its healthy period is beneficial for both an individual and the society. However, the prevailing views and approaches have not resulted so far in any significant extension of human lifespan and healthspan.

Improved living standards, medical and hygienic measures only increased the average life expectancy, which was achieved solely by reducing the number of infant deaths, accidental deaths and deaths caused by some pathological conditions and infections. The life extending effect of the so-called 'universal' anti-aging approach of caloric restriction observed in various model organisms is yet to be proven for human beings.

Neither has it been possible to develop effective biomarkers of aging. In addition to that, the anti-aging treatments available today have a rather inconsistent effect on human lifespan and healthspan. Quite often this effect is limited to the range established for non-specific compensatory responses, which casts doubt on whether they directly target the aging mechanisms.

IT CAN THEREFORE BE CONCLUDED THAT THE EXISTING APPROACHES ARE INSUFFICIENT FOR INCREASING THE MAXIMUM HUMAN LIFESPAN AND EXTENDING HEALTHY LONGEVITY.

Meanwhile, there has been an avalanche of new data about the role of specific genes in regulating lifespan of model animals, and about repeatable changes in expression of thousands of genes during aging of different tissues as a result of epigenetic structural adjustments. Regenerative medicine has achieved a number of spectacular successes as well, including reprogramming differentiated cells into stem cells, and identifying cytokines controlling cell differentiation.

New emerging knowledge has made it clear that gerontology needs some new approaches. We believe that the need for working out a complex interdisciplinary research program aimed at fight against aging has maturated in the scientific community. However, development methodology, program structure, collaboration principles have to be elaborated. A critical analysis of existing approaches, ideas and proposals is needed. Let us consider several approaches:

1 THE PRIORITY APPROACH

ONE ILLUSTRATION OF SUCCESSES ACHIEVED in fundamental gerontology is the approach proposed by the US government and a number of leading gerontologists at the summit of the National Institute on Aging in September 2008 in Gaithersburg, Maryland. This new approach is based on identifying the following priority areas:

SEARCH for healthspan markers. So far lifespan has been used as the main marker of slowing down the aging process. However, it is clear that increasing lifespan would be meaningless, and even counter-productive, if healthspan was not increased concomitantly. In order to achieve this it is important to understand what markers can be used to estimate healthspan, rather than just lifespan.

ADDRESS POTENTIAL differences in aging of mitotic versus postmitotic cells. Model animals used today (for example, adult nematodes and fruit flies) are comprised almost entirely of postmitotic tissues. New organisms, genetically tractable and with proliferative tissues as adults, need to be brought into the bestiary already being used.

STRENGTHEN THE FOCUS on cellular responses to stress. It has been established that the increased lifespan of many organisms has to do with the enhanced ability of their cells to adequately respond to stress.

THE ROLE OF INFLAMMATION as an emerging paradigm. Inflammation plays an important role in a number of age related diseases and pathologies. The number of inflammatory cytokines increases with age, which correlates with susceptibility to various diseases.

STEM CELLS AS AN ADDITIONAL new paradigm. The potential use of stem cell therapy in aging, including the possible use of induced pluripotent stem cells, requires a much deeper understanding of the normal biology of stem and precursor cells within an aging organism.

2 THE ENGINEERING APPROACH

THE DEVELOPERS OF THIS APPROACH believe that even without the knowledge of the fundamental causes of aging it is possible to dramatically slow down aging or even make it negligible by periodically repairing the age related damage accumulated in the organism. One example of this approach is the Strategies for Engineered Negligible Senescence (SENS), which identifies seven types of damage and possible ways of treatment:

REPLACING lost cells. There are three main ways in which cell loss can be countered. One is the natural stimulation of cell division, for instance cell division is naturally stimulated in some muscles by exercise. Another type of therapy is artificial administration of growth factors (for instance via injections) to stimulate cell division. In addition to that, cells can be modified in such a way as to make them divide more efficiently; such cells can then be introduced into the organism to replenish lost cells.

MAKING cancerous mutations harmless. It makes more sense to try and prevent chromosome mutations than to correct them. It is suggested that mutations should be prevented through 'whole body interdiction of lengthening telomeres, which would stop the development of cancer cells but would require periodic replacements of all the stem cells.

PREVENTING damage from mitochondrial mutations. Instead of correcting mitochondrial mutations it would be best to eliminate them completely. It is proposed to make copies of the 13 genes that are encoded by the mitochondrial DNA and move them completely within the cell nucleus.

REMOVING cells that the body tries but fails to kill – a number of cells such as visceral fat cells, senescent cells and some types of immune cells. 'Suicide' vaccines could be developed that would make such cells self-destruct without affecting other cells. Alternatively a targeted immune response could be induced to destroy such cells.

BREAKING extracellular cross-links. Chemicals could be developed that would break down the excessive cross-links between proteins without affecting any of the other chemical structures in the organism.

DESTROYING junk between cells. One solution would be to administer a vaccine stimulating the immune system to destroy the extracellular junk. Another approach is to use small molecules to destroy the plaques of molecular junk.

DESTROYING junk inside cells. Cells need to be allowed to break down the intracellular junk in place so it won't accumulate. This can be achieved by introducing the genes of additional enzymes capable of destroying the junk; such enzymes could be borrowed from some types of bacteria.

3 THE PROBLEM-ORIENTED

THE PROBLEM-ORIENTED approach focuses scientific research on the main problems and issues of aging biology. Another important aspect of this approach is that it consolidates the scientific community to discuss key issues, develop a common conceptual framework, and form the immortalistic worldview (a system of ideas based on an aspiration to at most postpone physical death relying on achievements of exact, natural and technical sciences).

HERE ARE A FEW SAMPLE QUESTIONS AND POSSIBLE ANSWERS TO THEM:

WHAT IS AGING?

1) Increase in the probability of death due to intrinsic biological causes.
2) Execution of a self-destruct program.
3) Homeostasis disruption on different levels of organization of life as a result of progressive failure in the functionality of the systems responsible for maintaining the stability of its internal environment.

WHY DO ORGANISMS experience a progressive and irreversible decrease in their physiological functions at the end of their life?

1) There is an aging program.
2) Catastrophic accumulation of random damage.
3) Antagonistic pleiotropy (aging quasiprogram).
4) 1, 2, or 3 depending on the type of a living organism.

WHAT ARE THE MECHANISMS RESPONSIBLE for the differences in life expectancy or the rate of aging within one species and between species?

1) Differences existing on the different levels of aging regulation, for example metabolism, stress resistance, tissue regeneration and cell death, and neurohumoral regulation.
2) Differences appearing on higher level of a living system organization during evolution.
3) Differences in the rate at which different organisms reach reproductive age.

WHY DO EXPERIMENTAL IMPACTS, like caloric restriction, delay the onset of a number of age-related physiological and pathological changes and increase the average and maximal life span in animals?

1) Hormesis (stimulating influence of moderate stress).
2) Metabolism slowing down.
3) Slowing down of development and the rate at which different organisms reach reproductive age (diapause).
4) Reduction in the toxic factors.

DO AGE RELATED CHANGES in the organism increase susceptibility to diseases or do diseases develop independently and exacerbate the effects of aging?

1) Yes, susceptibility to disease increases with age.
2) There is no aging as such, only a combination of pathological conditions.
3) Every organism experiences aging while age-related conditions only manifest in some individuals. Therefore it would be a mistake to equate age-related pathological conditions and the aging process itself.

WHAT STAGE OF EVOLUTION did aging emerge at or has it accompanied life from the moment that it first appeared?

1) Aging appeared at the same time as life (starting with the progenote).
2) It first appeared in one cell eukaryotes.
3) It first appeared in unitary multicellular organisms.
4) Aging emerges and disappears depending on the type of a living organism.

ARE AGING PROCESSES in an organism the result of aging on the cellular level?

1) Yes, and they are caused exclusively by cell aging.
2) Yes, but in addition there are tissue and systems levels of aging.
3) No, everything is determined by the systems level.

WHAT IS THE EXTENT to which aging is determined by genes?

1) Aging is completely determined by genes.
2) Aging is determined by external environmental factors and stochastic causes while the genotype plays a less prominent role.
3) The environment and genotype have equally important roles in aging.
4) Aging results from the predominant control and regulation of ontogenesis shifting from the genetic to the systems level after the organism reaches its reproductive age.

WHAT IS THE REASON for the existence of species with negligible aging?

1) Such species do not have aging programs.
2) The stress resistance mechanisms in these species are maximized while they are under no natural selection pressure to evolve towards early reproduction.
3) There are no such species.
4) Such species have completely different anti-aging programs.

HOW ARE REPRODUCTION and lifespan interrelated?

1) There is an inverse correlation between lifespan and reproduction (antagonistic pleiotropy and disposable soma theories).
2) Occasionally they are related while on other occasions there is no link.
3) Sex hormones are one of the main regulators of programmed cell death.

Other answers are possible. We believe this scope of questions needs to be more detailed to such an extent at which it can be verified in experiments. This could give us an opportunity to work out the "agenda" of unsolved problems of aging biology.

4 STRENGTHENING THE HOMEOSTASIS/ HOMEODYNAMICS

AGING, SENESCENCE AND DEATH are the final manifestations of unsuccessful homeostasis or failure of homeodynamics. A wide range of molecular, cellular and physiological pathways of repair and their interactions give rise to a "homeodynamic space" or the "buffering capacity", which is the ultimate determinant of an individual's chance and ability to survive and maintain a healthy state. A progressive shrinking of the homeodynamic space, mainly due the accumulation of molecular damage, is the hallmark of aging and the cause of origin of age related diseases. A critical component of the homeodynamic property of living systems is their capacity to respond to stress in order to counteract, adapt and survive. It is this homeodynamic space as a whole or the individual components of the homeodynamic machinery, which can be the targets of interventions by strengthening the homeodynamics. Thus it is suggesgted that if biological systems are intentionally exposed to mild stress (for example, exercise), so that their homeodynamic pathways of maintenance and repair get challenged, and in response become strengthened, this should lead to achieving beneficial hormetic effects, including health- and longevity-promotion.

5 CANCELLING THE AGING PROGRAM

CANCELLING THE AGING PROGRAM. Some researchers believe our bodies may be programmed to age. If an aging program actually exists then it must be identified and shut down. In this case there would be no need to look for and eliminate each of the consequences of aging as proposed in the engineering and priority based approaches. For example, some scientists believe that such a "program of aging" is governed by the "biological clock" whose activity is regulated by epiphysis and hypothalamus. However, it is possible that no specific aging program really exists, but there is instead a stable quasiprogram also known as 'antagonistic pleiotropy', where the key genes controlling metabolism, growth and the development of the organism have long-term side effects that result in aging.

6 A UNIFIED SYNTHETIC THEORY OF AGING

CREATION OF A UNIFIED SYNTHETIC THEORY of aging in the evolutionary-comparative aspect. The unified theory of aging should consider numerous factors, the most important of which are evolution and comparative biology. The exposition form can, for example, be a set of schemes and tables describing the aging processes on different levels of organization of life for different types of tissues (proliferative, postmitotic) and for different types of animals taking evolutionary aspect into account.

7 THE SCREENING APPROACH

THERE IS ALSO a proposition to screen 100, 000 chemical compounds on mice or other suitable animals in order to reveal their geroprotective properties (the search method or the screening approach). The authors of this idea start from the assumption that a simple screening would lead to a positive result faster, than the actions based upon analytical work, due to the lack of knowledge and understanding of human metabolism.

TOTAL APPROACH

WHILE CREATING THE COMPLEX interdisciplinary "Human Life Extension" program the "Science for Life Extension" Foundation presumed that most likely there is no contradiction among all the listed approaches and it is necessary to take all of them into account and address the problem in different ways. We also propose to consider defeating aging as not only a research, but as a technological problem in the first place.

SO, THE "HUMAN LIFE EXTENSION" PROGRAM PROPOSES A TOTAL APPROACH, WHICH COMPRISES SEVERAL METHODOLOGICAL PROBLEMS AND APPROACHES, ACTUALIZED IN THE PROGRAM. THEIR SIMULTANEOUS IMPLEMENTATION IS SUGGESTED:

DEVELOPING NEW METHODOLOGIES FOR STUDYING AGING AND STRESS RESISTANCE. It is obvious that a breakthrough in any field of research is intercon-

nected with development of new technologies and methodologies. The study of aging and stress resistance needs to undergo a number of technological improvements based on the use of new instruments and bioinformatics methods as well as new model systems. Because aging is a systemic condition, priority must be given to population wide research into age-related changes occurring at the level of complete metaboloms, proteomes, genomes, epigenomes and physiomes. It is also necessary at this stage to develop a universal language for describing verified facts, experimental results and research protocols. At this point this represents a significant problem because there are no generally accepted definitions of aging, healthy longevity and age-related pathologies.

STUDYING AGING AND STRESS RESISTANCE MECHANISMS IN MODEL ANIMALS. At present biogerontology is going through a stage of intensive data collection. At this stage it is necessary to take inventory of the ideas about the nature of aging that are available today and to test these ideas experimentally. While research into systemic changes must continue (changes at the level of cytokines, hormones, metabolites, damaged structures), special attention has to be paid to tissue specific features of aging and stress resistance as well as to the difference in aging of stem cells, proliferative cells and postmitotic somatic cells.

STUDYING THE EVOLUTIONARY AND COMPARATIVE ASPECTS OF AGING AND ANTI-AGING. Once new aging mechanisms have been identified in model animals the next logical step is to look for their counterparts in humans. However, comparisons between similar species with significantly different maximum life spans are equally important, as well as comparisons between evolutionary distant groups aimed at identifying the most conservative aging mechanisms and manifestations. In addition to this, the differences in aging between individual specimens from the same species should also be studied, including stochastic differences (when both the genotype and environmental conditions are more or less the same). This stage should result in the development of a unified theory of aging based on comparative and evolutionary studies.

MODELING AGING AND ANTI-AGING PROCESSES. The huge amounts of data collected in the previous stages should undergo integrated bioinformatics analysis which must include: modeling the molecular aging regulating systems (gene networks of metabolism, stress response systems, interaction between stem cells and their niches, mechanisms of neurohumoral regulation); developing mathematical models of age-related changes in the homeo-dynamics of different systems in the organism; creating aging models for different levels of integration of biosystems (molecular, cellular, organ-tissue level, systems level, organism level); developing mathematical models of specific age-related pathological conditions.

IDENTIFYING THE KEY POINTS FOR APPLYING THERAPIES. Modeling aging and anti-aging processes will make it possible to develop a detailed conceptual model of aging which will help identify the processes and systems that are the most vulnerable to aging and at the same time the most accessible to therapies. This stage should result in the creation of a road map for cancelling aging. To understand what specific steps are needed to defeat aging, this complex task has to be broken down into several subtasks each of which should be further subdivided into more specific steps. In this way a multilevel road map will be created which will define specific steps which must be taken to cancel aging.

DEVELOPING METHODS FOR EVALUATING AND PREDICTING THE BIOLOGICAL AGE AND THE EFFECTIVENESS OF THERAPIES. No therapy, whether it is based on genetic engineering, environmental modifications or the use of drugs, can be applied adequately unless there are methods for evaluating its effectiveness. For this purpose new precise biometrics need to be found to evaluate the aging process and the biological age of an individual. Eventually a system of differential equations will have to be developed that would make it possible to predict the effectiveness of any type of interference in the aging process.

DEVELOPING TECHNOLOGIES FOR INTERFERING IN THE AGING AND ANTI-AGING PROCESSES. Once key points for interference have been identified and methods for assessing the effectiveness of interference have been developed the next stage will be to develop specific technologies for interfering in the aging and anti-aging processes, which would eventually lead to development of therapies that will increase both life span and healthspan of human beings.

THEREFORE, THE COMPLEX INTERDISCIPLINARY "HUMAN LIFE EXTENSION" PROGRAM HAS BEEN DEVELOPED TO COORDINATE THE EFFORTS OF DIFFERENT GROUPS OF RESEARCHERS

that encounter different aspects of aging on molecular, sub-cellular, cellular, organ, system and population levels in their biochemical, genetic, environmental, demographic and medical studies. The implementation of the total approach will make it possible to model aging processes at different levels of integration of biosystems and develop a set of practical measures aimed at cancelling aging.

WE OFFER SELECTED PROPOSALS OF THE "HUMAN LIFE EXTENSION" PROGRAM AND WELCOME EXPERTS FOR COLLABORATION ON CREATING SCIENTIFIC STRATEGIES AGAINST AGING.

PROGRAM AIMS AND OBJECTIVES

MAIN AIM: DEVELOPMENT AND APPLICATION OF SCIENTIFIC METHODS IN ORDER TO SUBSTANTIALLY EXTEND HUMAN HEALTHY LIFESPAN

PRIORITY OBJECTIVES

1. Research in fundamental mechanisms of aging
2. Development of methods for intervention in the aging process in order to slow it down
3. Practical application of the scientific findings in order to substantially extend human healthy lifespan

STEP-BY-STEP ACTIONS

1. Drawing up a complex interdisciplinary proposal for research into aging mechanisms
2. Defining the essential forms and means of international cooperation for the implementation of the proposal
3. Defining the essential forms and means of international cooperation for the implementation of the proposal
4. Concluding an international agreement about cooperation on research into aging
5. Implementing the plan and achieving its priority objectives

CONTENT

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Section **1**

AGING AND EVOLUTION

IN EVOLUTIONARY TERMS, aging is an emergent phenomenon that takes place primarily in protected environments which allow survival beyond the natural lifespan in the wild. The natural lifespan of a species, termed "essential lifespan" (ELS), or the "warranty period, is the time required to fulfill the Darwinian purpose of life in terms of successful reproduction for the continuation of generations.

Species that undergo fast maturation and have an early onset of reproduction with large reproductive potential generally have a short ELS, whereas slow maturation, late onset of reproduction, and small reproductive potential of a species is concurrent with its long ELS. Novel evolutionary interpretations have given rise to the notion of "post-reproductive genetics" as an explanation for different biological roles played at different ages by the same genetic variants.

Understanding aging in the context of evolutionary basis of life history traits of different species is necessary for developing species-specific aging interventions.

(A) BASIC RESEARCH ASPECTS

A.1. ALREADY ESTABLISHED FACTS

1.1. Cross-species and intra-species variations in lifespan

1.2. Negligible, rapid and progressive senescence

1.3. Theories of evolution of aging and longevity

1.4. Genetic selection through delayed reproduction for longevity extension

A.2. MAIN UNSOLVED QUESTIONS

2.1. How to validate the 'evolution of senescence' hypotheses and models in molecular mechanistic terms?

2.2. What are the mechanisms of inter- and intra-species variation in lifespans?

2.3. Can the study of molecular mechanisms governing the life-spans of long-lived organisms be extended/extrapolated to increase human life-span?

2.4. Is human lifespan extension viable? What is the prognosis of possible human biological evolution in this context?

2.5. What are the evolutional costs of lifespan extension?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Analysis of changeability limitations and evolutional taboos in the context of possible elimination of aging

3.1.1. Possibility of non-aging as one of the evolutional taboos

3.1.2. Analysis of available versions of changeability limitations and evolutional taboos classifications

3.1.3. Evaluation of confines to human biological evolution.

3.2. Evaluation of biological distinctions of long-lived animals in the context of possible after-effects of human life extension – in particular population growth rate and digenesis

3.2.1. Data acquisition about diversity of long-lived species

3.2.2. Population growth rate of long-lived organisms

3.2.3. Data acquisition about digenesis in populations of long-lived organisms

3.2.4. Evaluation of other biological distinctions of the long-lived organisms that may be of importance for understanding the after-effects of human life span increase.

3.3. Evaluation of regularities in aging alterations in the evolution process of organisms. Critical overview of the examples of "non-aging" organisms

3.3.1. Specification of the correlation between the natural evolution of aging and directed evolution

3.3.2. Characterization of aging in organisms of different organization levels.

3.3.3. Systematization of the examples of "non-aging" organisms in correlation with general laws of animal diversity in order to elicit aging evolution tendencies.

3.3.4. Reliability estimation of reports on existence of "non-aging" organisms

3.4. Evaluation of possible changes in the biosphere in case of human aging elimination program realization

3.4.1. Evaluation of main trends in the current changes in the biosphere (natural complexes degradation, population growth, increase in the number of technical objects).

3.4.2. Evaluation of possible changes in the biosphere load in case of human aging elimination program realization.

3.5. Evaluation of species aging phenomenon

3.5.1. Characterization of the main species extinction interpretations in the cause of biosphere evolution.

3.5.2. Evaluation of *Homo sapiens* species aging

3.5.3. Impact of elimination of individual aging on species aging

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. DEVELOPMENT OF EVOLUTIONARY THERAPEUTICS AGAINST POST-GENETIC CONDITIONS

B.2. DEVELOPING LIFE-HISTORY BASED TREATMENTS FOR BIOLOGICAL FUNCTIONS IN DIFFERENT SPECIES

B.3. PERSONALISED MEDICINE IN THE FRAMEWORK OF EVOLUTIONARY HISTORY

Section **2**

MOLECULAR GENETIC ASPECTS OF AGING AND LONGEVITY

ACCORDING TO THE EVOLUTIONARY theories of aging and longevity no specific gerontogenes have evolved with a sole purpose of causing aging and determining the lifespan of an individual. However, genes do influence aging and longevity, and it is the combination of genes, milieu and chance that are the determining factors. The contribution of genes in the inheritance of longevity is considered to be about 25%. At the species level, the role of genes is mainly in creating a homeodynamic space for assuring a lifespan essential for successful reproduction, in accordance with the evolutionary history of a species.

The polygenic nature of life history traits and survival abilities raises several challenges with respect to aging research and interventions.

(A) BASIC RESEARCH ASPECTS

A.1. ALREADY ESTABLISHED FACTS

1.1. The evolutionary nature of aging and longevity genes
- **1.1.1.** Longevity assurance genes
- **1.1.2.** Virtual gerontogenes

1.2. Natural and induced genetic mutants of aging and longevity in:
- **1.2.1.** Yeast
- **1.2.2.** *C. elegans*
- **1.2.3.** *Drosophila*

1.3. Genes involved in regulating replicative senescence

1.4. Human mutants for accelerated ageing
- **1.4.1.** Progeria
- **1.4.2.** Werner's syndrome

1.5. Transgenic manipulations for enhanced longevity
- **1.5.1.** Yeast
- **1.5.2.** *C. elegans*
- **1.5.3.** *Drosophila*
- **1.5.4.** Rats and mice

1.6. Gene association with longevity
- **1.6.1.** Centenarians
- **1.6.2.** Monozygotic and dizygotic twins

A.2. MAIN ISSUES TO BE RESOLVED

2.1. How many genes make an effective homeodynamic space?

2.2. What is the hierarchy within the genes for maintenance and repair?

2.3. Which genes directly affect the rate of aging and which genes have only indirect effects on aging and longevity?

2.4. What are the genome wide associations with aging and longevity?

2.5. How does gene polymorphisms relate to the functional capacity during aging?

2.6. What are the genetic markers of health?

2.7. Can individual lifespan be predicted?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Further identification of longevity assurance genes in animals and humans
- **3.1.1.** Stress response pathways
  - **3.1.1.1.** Chaperones
  - **3.1.1.2.** Autophagy
  - **3.1.1.3.** Antioxidants
  - **3.1.1.4.** DNA repair
  - **3.1.1.5.** Inflammation
- **3.1.2.** Metabolic rate regulators
  - **3.1.2.1.** Insulin response
  - **3.1.2.2.** Sirtuin response
  - **3.1.2.3.** Mitochondrial electron transport
  - **3.1.2.4.** Protein synthesis
  - **3.1.2.5.** Protein modifications
  - **3.1.2.6.** Protein degradation

3.2. Longevity gene polymorphism and its functional relevance in:
- **3.2.1.** Healthy and diseased elderly
- **3.2.2.** Genetic interactions and compensation
- **3.2.3.** Population differences in longevity gene polymorphisms

3.3. Genetic indices of frailty and vulnerability
- **3.3.1.** Genes involved in maintaining homeodynamic space
- **3.3.2.** Genes for muscle strength and muscle mass

3.4. Genetic indices of mental health and well being with aging
- **3.4.1.** Genes involved in maintaining short term memory
- **3.4.2.** Genes involved in maintaining long term memory
- **3.4.3.** Genes to counteract depression and mood swings

3.5. Gene networks reconstruction
- **3.5.1.** Stress response gene network
- **3.5.2.** Redox-regulation gene network
- **3.5.3.** Cell cycle gene network
- **3.5.4.** Apoptosis gene network
- **3.5.5.** Antioxidant defense gene network
- **3.5.6.** Glucose homeostasis gene network
- **3.5.7.** Lipid metabolism gene network
- **3.5.8.** Age-associated pathologies gene network
- **3.5.9.** Circadian cycle gene network
- **3.5.10.** Immune response gene network
- **3.5.11.** Neuro-endocrine signalling

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. PERSONALIZED MEDICINE

- **1.1.** Determination of genetic profiles for health, survival and longevity, and preparing personlised programme for intervention
- **1.2.** Genetic profile-based counselling to reduce/counter the impact of presence of genetic markers

B.2. MOLECULAR INTERVENTIONS THROUGH FUNCTIONAL FOOD, NUTRICEUTICALS AND DRUGS TO:

- **2.1.** neutralise the genetic deficiencies for healthy longevity
- **2.2.** enhance genetic abilities for healthy longevity

B.3. NANOCHIP DEVELOPMENT TO TEST INDIVIDUAL SENSITIVITY TO GEROPROTECTORS AND FOOD SUPPLEMENTS

B.4. POPULATION-TARGETED METHODS FOR RETROSPECTIVE AND PROSPECTIVE TESTING FOR HEREDITARY PREDISPOSITIONS

Section **3**

CELLULAR AGING AND REPLICATIVE SENESCENCE

IN MODERN BIOGERONTOLOGY, the terms "cellular aging", "cell senescence", or "replicative senescence" imply the study of normal diploid cells in culture, which during serial subcultivation undergo a multitude of changes culminating in the permanent cessation of cell division. This process of cellular aging *in vitro* is generally known as the Hayflick phenomenon, and the limited division potential of normal cells is called the Hayflick limit. The Hayflick system of aging of normal diploid differenatiated cells in culture has proved to be in the basis for developing the cellular and molecular understanding of the overall process of aging. A loss of proliferative capacity of any of the cell types has a deteriorative impact on the functioning and survival of the entire organism.

Occurrence of fully senescent or near-senescent heterogenous cells *in vivo* can promote dysfunctioning of the other tissues by producing harmful signals, and can also promote and stimulate the growth of other precancerous and cancerous cells.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Universal occurrence of the Hayflick limit in normal diploid differentiated cells

1.2. Molecular basis of the Hayflick limit
- **1.2.1.** Progressive loss of global DNA methylation
- **1.2.2.** Progressive loss of telomeres

1.3. The nature of the replicative senescence – check point regulation

1.4. Modes of cellular transformation and immortalisation

1.5. Structural and functional changes in cells during aging
- **1.5.1.** Reduced rates of cell proliferation and growth
- **1.5.2.** Reduced cell motility
- **1.5.3.** Reduced stress response
- **1.5.4.** Enhanced sensitivity to toxins and radiation
- **1.5.5.** Altered cytoskeleton and cell morphology
- **1.5.6.** Enhanced lysosomal residual bodies and other debris

1.6. Biochemical changes in cells during aging
- **1.6.1.** Reduced amounts and activities of numerous enzymes
- **1.6.2.** Increased amounts and activities of numerous enzymes
- **1.6.3.** Reduced production and turnover of ATP

1.7. Molecular changes in cells during aging
- **1.7.1.** Accumulation of damage in nuclear and mitochondrial DNAs
- **1.7.2.** Accumulation of abnormal proteins
- **1.7.3.** Altered gene expression (mRNA levels)
- **1.7.4.** Altered protein expression

A.2. THE MAIN UNSOLVED QUESTIONS

2.1. Do replicatively senescent cells exist in vivo?

2.2. How senescent cells affect the surrounding tissue?

2.3. Does progressive aging of cells has physiological consequences?

2.4. What is the functional relevance of specific molecular damage?

2.5. What is the nature of protein interactions during aging?

2.6. Is telomere loss cell-type- and chromosome-specific?

2.7. Does repeated proliferation of stem cells induce any aging changes?

2.8. What are the optimal in vivo-like culturing conditions for normal cells?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Existence of pre-senescent and senescent cells in vivo
- **3.1.1.** Identifying and visualizing cells at different age levels in vitro and in vivo
- **3.1.2.** Establishing the functional age of cells in vitro and invivo by functional bio-markers
- **3.1.3.** Correlating the proportion of senescent cells with the extent of physiological deterioration

3.2. Programmed cell death – apotosis and aging
- **3.2.1.** Occurrence of spontaneous and induced apoptosis in aging cells
- **3.2.2.** Consequences of reduced apoptosis in senescent cells

3.3. Molecular damage and heterogeneity during celluar aging
- **3.3.1.** Correlating different types of nuclear DNA damage to specific consequences
- **3.3.2.** Correlating different types of mitochondrial-DNA damage to specific consequences
- **3.3.3.** Inter-molecular hierarchy to vulnerability to damage
- **3.3.4.** Detailed proteomic patterns during cellular aging
- **3.3.5.** Detailed post-translational modification patterns during cellular aging
- **3.3.6.** Detailed non-coding sRNAs and iRNAs patterns during cellular aging
- **3.3.7.** Genetic networks and profiles during cellular aging
- **3.3.8.** Protein-protein interaction profiles and signatures during cellular aging
- **3.3.9.** Netwrok interruptions and formation of illegitimate networks during cellular aging
- **3.3.10.** Consequences of damage accumulation in transcription factors on downstream gene expression
- **3.3.11.** Significance of mitochondrial heterogeneity
- **3.3.12.** Changing stress response profiles during cellular aging
- **3.3.13.** Immediate and delayed stress responses during cellular aging

3.4. Clinical applications of cellular senescence
- **3.4.1.** Selective induction of senescence in early and advanced tumours
- **3.4.2.** Selective reactivation of telomerase in senescent cells
- **3.4.3.** Telomeric length determination for biological age
- **3.4.4.** Telomerase activity determination for cancer diagnosis
- **3.4.5.** Cornea and oral cavity cell senescence via telomere-independent pathways
- **3.4.6.** Cellular senescence in imbalanced T-cell populations

3.4.7. Cellular sensenscence in sarcopenia
3.4.8. Cellular senescence in osteoporosis
3.4.9. Angiogenesis and endothelial cell senescence
3.4.10. Senile retinopathy and senescence
3.4.11. Cellular senescence and chronic inflammation

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

1. Sensecent cell detection kits for determining biological age status
2. Telomere length determination kit and longevity probabilities
3. Using the Hayflick system for testing novel anti-aging compounds for nutriceutical applications.
4. Using the Hayflick system for testing novel anti-aging compounds for cosmetic developments
5. Screening and testing for novel compounds for promoting wound healing, angiogenesis, differentiation.
6. Developing multi-culture systems as in vitro tissue equivalents for drug screening

Section **4**

STEM CELLS AND AGING

THE UBIQUITOUS NATURE and presence of stem cells has become both a beacon and a challenge. It is the seemingly endless potential of stem cells to renew themselves, to differentiate into various cell types and to participate in tissue repair and regeneration that makes them very attractive for aging research and interventions. Presently, stem cells form the basis of the so-called regenerative medicine. This is because the fundamental causes of the aging of the body, organs and tissues reside in the aging of the cells and the macromolecules within them. While a lot of information on stem cells and their niches, and their various functional capabilities has been collected in animal studies, we are still far from understanding their molecular mechanisms and intricate relationship within the human body, location and specific cell type.

Similarly, there is much to be learnt about the aging of stem cell niches and their relationship with the changing microenvironments. However, this field of stem cell-based anti-aging interventions is a highly promising and rapidly developing area.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Stem cell niche hypothesis and confirmation of its presence
- **1.1.1.** Demonstrated in *C. elegans*
- **1.1.2.** Demonstrated in *Drosophila*
- **1.1.3.** Examples of discrete "niches" have paved the way for identifying and characterizing stem cell niches in vertebrates
- **1.1.4.** Stromal niches
- **1.1.5.** Epithelial niches

1.2. Strategies and techniques to establish stem cells and putative niches
- **1.2.1.** Lineage-tracing techniques – identification of stem cell populations in tissues such as:
  - **1.2.1.1.** Nervous system
  - **1.2.1.2.** Gonads
  - **1.2.1.3.** Digestive system
  - **1.2.1.4.** Skin
    - **1.2.1.4.1.** Microenvironments such as epidermis
    - **1.2.1.4.2.** Hair follicles
    - **1.2.1.4.3.** Sebaceous glands
  - **1.2.1.5.** Intestinal system (colon crypts)
- **1.2.2.** Single-cell transplantation – whereby isolation of cells by the FACS technique together with transplantation has identified stem cells from solid tissues such as:
  - **1.2.2.1.** Testis
  - **1.2.2.2.** Muscle
  - **1.2.2.3.** Breast
  - **1.2.2.4.** Prostate
- **1.2.3.** Real-time imaging of stem cell niche interactions have identified stem cell niches in:
  - **1.2.3.1.** Drosophila ovaries
  - **1.2.3.2.** Drosophila neuroblasts
  - **1.2.3.3.** Murine testis

1.3. Functional characterization of the niche
- **1.3.1.** Ablation
- **1.3.2.** Expansion
- **1.3.3.** Repair
- **1.3.4.** Gain- and loss-of-function studies have shown that hematopoietic stem cells (HSCs) receive information from various cells such as:
  - **1.3.4.1.** Endosteal
  - **1.3.4.2.** Endothelial
  - **1.3.4.3.** Advential
  - **1.3.4.4.** Adipocytes
  - **1.3.4.5.** Other support cells
- **1.3.5.** Tissue Regeneration
- **1.3.6.** Involvement of genetic factors
- **1.3.7.** Role in disease
- **1.3.8.** Role in Cancer

1.4. Relationship with aging – intrinsic changes in stem cells
- **1.4.1.** Maintenance of proliferative ability
- **1.4.2.** Maintenance of responsiveness
- **1.4.3.** Maintenance of cell cycle regulation

1.5. Relationship with aging – changes in niche function
- **1.5.1.** Reduced tissue homeostasis
- **1.5.2.** Reduced repair ability
- **1.5.3.** Reduced regenerative ability

A.2. THE MAIN UNSOLVED QUESTIONS

2.1. Do stem cells undergo any intrinsic age-related changes, such as occurrence and accumulation of molecular damage?

2.2. What are their changes in stem cell niches during the course of aging and how can these be directly correlated with loss of regenerative and repair potential?

2.3. What is the relationship of cancer stem cells with disease and aging?

2.4. Can we study the molecular mechanisms of immortal human stem cells, non-dependent of a niche, for detection of targets and models of anti-aging?

2.5. Can stem cells restore organ or tissue function irrespective of the state of the rest of the body?

2.6. Can induced pluripotent stem cells be made from cells obtained at all ages?

2.7. How to convert induced pluripotent stem cell to specific cell types within the context of aging?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Study of stem cells and their specific niches: "aging" as a process of loss of the organism's regeneration potential and manifestation of the aging phenotype
- **3.1.1.** Genetic features of regional stem cells in the process of aging of the organism

3.1.1.1. Genes defining stem cells' regenerative potential, including:

3.1.1.1.1. cell cycle regulating genes (pRB/p53)

3.1.1.1.2. genes defining cyto- & nuclear skeleton structure (collagen, lamin A/C)

3.1.1.1.3. genes of interferon range, which relate to IGF family,

3.1.1.1.4. MAP kinases

3.1.1.1.5. antioxidant defense genes

3.1.1.1.6. proliferative activity regulating genes (incl. Pou5fl (Oct3/4), Utfl, Tdgfl (Cripto)

3.1.1.1.7. Wnt

3.1.1.1.8. Stat

3.1.2. Gene expression governing proliferative potential of different types of stem cells during aging

3.1.3. Factors of DNA stability and search for the ways to preserve and enhance abilities of DNA repair of different types of stem cells in adult organisms

3.1.3.1. Already discovered enzymes (e.g., Lig4) which need an activation to ensure better stem cells' DNA repair in the process of aging

3.1.3.2. Changes which occur in the system of stem cells' DNA repair of an adult organism (decrease both of DNA double-strands' and single-strand breaks repair, etc.)

3.1.3.3. Other DNA repair proteins, which are losing activity over the time

3.1.4. Epigenetic changes of stem cells during aging (methylation of DNA, deacetylation and methylation of histones, irreversible changes of chromatin et al.)

3.1.5. Effect of niche cells on aging of regional stem cells and search for signalling pathways and molecules which allow to effect niche cells to restore stem cells regeneration potential.

3.1.5.1. Effect of stromal cells of the marrow tissue on aging of hematopoietic stem cells.

3.1.5.2. Detection of specific cell niches for all known human stem cells types

3.1.5.3. Ability of the niche cells to support the regeneration potential of individual stem cell populations through:

3.1.5.3.1. secretion of growth-stimulating factors (e.g. BMPs (bone morphogenic proteins)

3.1.5.3.2. secretion of cytokines and chemokines

3.1.5.3.3. secretion of the non-protein substances

3.1.5.3.4. changes in intercellular contact parameters

3.1.5.3.5. changes in basal membrane and extracellular parameters

3.1.5.3.6. mechanistic impact on stem cells

3.1.5.3.7. interaction with capillary endothelium cells

3.1.5.3.8. changes in physical parameters of intercellular environment (oxygen and carbon dioxide partial pressure, pH etc.)

3.1.5.4. Effect of P-selectin and other adhesion molecules which ensure integrity of contacts between niche cells and stem cells, on the aging rate of stem cells

3.1.5.5. Methods of impacting niche cells to increase the repair potential of stem cells, which do not interfere with internal signaling pathways of the stem cells, aimed at reduction of their tumorigenicity.

3.2. Development of methods and techniques for preservation of regional stem cells of a young organism for their possible future application

3.2.1. Development of preservation methods for the following types of available regional stem cells:

3.2.1.1. hematopoietic and mesenchymal (stromal) stem cells from umbilical blood

3.2.1.2. stromal stem cells from the placental complex

3.2.1.3. dental pulp stem cells

3.2.1.4. hair follicle stem cells

3.2.1.5. endometrium mesenchymal cells;

3.2.1.6. other types of stem cells, which require more invasive collection procedures, including bone marrow stem cells

3.2.2. Development of methods of collection, processing, and testing of the sample cell material

3.2.3. Development of methods of cryopreservation and thawing of the sample material

3.2.4. Elaboration of techniques of cell culture using bioreactors and synthetic media to minimize human factor.

3.3. Study of cancer stem cells and development of methods to control and treat tumor progression

3.3.1. Setting up research for screening for tumor stem cells within specific tissue tumor types (e.g. for some types of mammary tumor and gliomas there have been detected tumor stem cells (CD133+).

3.3.2. Allocation from primary tumor cells, resistant to chemo- or radiotherapy, a population which is capable to self-renewal in vivo.

3.3.3. Development of methods of impacting tumor stem cells in order to differentiate them and increase their sensitivity to therapeutic treatment.

3.4. Study of the potential of stem cells to restore organ or tissue functions lost due to aging

3.4.1. Possible use of stem cells for the treatment of age-related neurodegenerative diseases

3.4.1.1 Experimental and clinical research of cell-specific application (neurons, oligodendrocytes obtained from different sources including iPS,

etc) for the treatment of pathologies related to neuron dysfunction (Parkinson's disease, secretion of DOPA by dopaminergic neurons) neuronal loss (Alzheimer's disease) or other CNS cell types (Motor Neuron Disease, Multiple Sclerosis)

3.4.2. Capability of stem cells for the treatment of age-related diseases associated with loss of myocardium function and tissue blood supply

3.4.2.1. Determination of existence of myocardial stem cells and methods to promote cardiac regeneration

3.4.2.2. Development of a technique to produce cardiomyocyte precursors from human embryonic stem cells or their equivalents (iPS cells with induced pluripotency)

3.4.2.3. Initiation of clinical studies of cellular and genetic effects (CD133, VEGF gene, FGF etc.) conducted in order to choose most effective therapy methods under different ischemia nosologies (e.g. atherosclerosis of lower extremities, diabetic foot, myocardial ischemia etc.)

3.4.3. Application of stem cells for the treatment of age-associated diseases related to deterioration of musculoskeletal system.

3.4.3.1. Initiation of clinic research of bone tissue and articular cartilage regeneration using autologous mesenchymal stem cells which are able to differentiate into precursors of bone and cartilage tissue

3.4.3.2. Initiation of research aimed to generate mesenchymal stem cells from fat tissue.

3.5. Study of molecular mechanisms of immortal human stem cells, independent of a niche, for detection of targets and models of anti-aging

3.5.1. Protein and genetic factors that promote pluripotency of mESC (mouse embryonic stem cells) and hESC (human embryonic stem cells).

3.5.1.1. In regulation of telomeres length and activity of telomerase complex enzymes

3.5.1.2. In regulation of cell cycle (decrease of activity of p53 and Rb genes),

3.5.1.3. In genome stability and in high activity of repair enzymes,

3.5.1.4. In epigenetic stability of the ESC genome.

3.5.2. Development of large scale culture techniques of hESC and their derivatives and in vitro differentiation protocols in defined conditions in the absence of multifactor components.

3.5.3. Study of hESC differentiation potential for their further application for maintenance of different functions of a human body.

3.5.3.1. Possible use of differentiated hESC to restore integrity of CNS lesions (oligodendrocytes secreting basic myelin protein, disseminated sclerosis, trauma)

3.5.3.2. Possibility to generate dopaminergic neurons for transplantations for patients with Parkinson's disease.

3.5.3.3. Possible use of vascular endothelium cells or their precursors for the treatment of pathologies associated with the vasculature including age-related pathologies.

3.5.3.4. Protocols of hESC differentiation into hematopoietic or differentiated blood cells.

3.5.3.5. Characterizing hESC lines in cell banks to generate a standardized and inexhaustible source for blood-producing cells.

3.5.3.6. hESC differentiation into neuroepithelium, including pigmented photoreceptor neuroepithelium, which will allow a breakthrough in treatment of age-related ocular diseases.

3.5.3.7. Possibility to differentiate hESC into insulin-producing beta cells.

3.5.3.8. hESC differentiation to cardiomyocytes and the development of modes of transmission (imposition, electro-mechanic programming) of pacemaker activity

3.5.4. Research directed to solve problems associated with the use of hESC for therapeutic purpose:

3.5.4.1. Techniques of selecting differentiated derivatives from undifferentiated ES cells to reduce potential tumor formation

3.5.4.2. Establishing a full-scale bank of hESC lines which are fully compatible with their recipients, similarly to bone marrow donor banks and other tissue and organ banks.

3.5.4.3. Possible adaptation of the parthenogenesis method, which was developed for primates, to humans.

3.5.4.4. Possibility to obtain hESC using the method of somatic (adult) cell nucleus transfer. Verification of the theory which states that obtained ESC "inherit" the "age" of the genetic material of the somatic (adult) cell (age defects, either accumulated stochastically or programmed epigenetically).

3.6. Study of ips cells or cells with induced pluripotency (cells which being influenced by certain exogenous factors can be brought to esc-like cells)

3.6.1. Possibility to genetically re-program recipient's somatic cells.

3.6.2. Developing highly effective techniques which allow for epigenetic reprogramming in the absence of viral vectors and proto-oncogenes to reduce safety risks.

3.6.3. Immortality of the genetically induced pluripotent stem cells in culture in vitro.

3.7. Working out protocols for induced differentiation of pluripotent stem cells (ipsc) into functional cells of different types in order to use them for regaining organ-tissue functions lost due to aging and treating age-associated pathology including:

3.7.1. In the frame of cell therapy.

3.7.1.1 Substitutive;
3.7.1.2 Reparative;

3.7.2. Not in the frame of cell therapy.

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. REGENERATIVE MEDICINE

- **1.1.** Using stem cell therapy to regenerate dead tissue or rejuvenate aging cells
- **1.2.** Replenishment of falling cell numbers, for example neurons to improve memory retention at old age
- **1.3.** Directing substitutive modes or reparative modes
- **1.4.** Organ specific regeneration under in vitro or in vivo conditions
- **1.5.** Spare parts factory

B.2. CELL BANKING

- **2.1.** Market for technologies to enable suitable stem cell storage facilities
- **2.2.** Market for stem cell viability test assays
- **2.3.** Market for healthy donor stem cell banks
- **2.4.** Market for self-donor stem cell banks where individual donates his stem cells only for personal use as insurance against potential disease in the future

B.3. MEDICAL INTERVENTIONS

- **3.1.** Stem cells as intrinsic biological markers of the "real-age" of an individual
- **3.2.** Medical intervention strategies for curing debilitating disease such as:
  - **3.2.1.** Stroke
  - **3.2.2.** Diabetes
  - **3.2.3.** Alzheimer's
  - **3.2.4.** Parkinson's
  - **3.2.5.** Sarcopenia
  - **3.2.6.** Muscle dystrophy
- **3.3.** Pharmaceutical and nutriceutical factors factors that change microenvironment of stem cell niches
- **3.4.** Diagnostic kits of extrinsic and intrinsic factors as molecular biomarkers of disease prediction

Section **5**

HORMESIS

HORMESIS IN AGING is defined as the life supporting beneficial effects resulting from the cellular responses to single or multiple rounds of challenge. The key conceptual features of hormesis are the disruption of homeodynamics, the modest overcompensation, the reestablishment of homeodynamics and the adaptive nature of the process. An example of stress-induced hormesis is the well-documented beneficial effects of moderate exercise as a hormetic agent, which initially increases the production of free radicals, acids and aldehydes.

(A) BASIC RESEARCH ASPECTS

A.1. ALREADY ESTABLISHED FACTS

1.1. Hormetic anti-aging effects in different aging model systems
- **1.1.1.** Nematodes
- **1.1.2.** Drosophila
- **1.1.3.** Rats and mice
- **1.1.4.** Human cells

1.2. Hormetic agents - hormetins
- **1.2.1.** Physical hormetins
  - **1.2.1.1.** Heat shock
  - **1.2.1.2.** Cold shock
  - **1.2.1.3.** Ionizing radiation
  - **1.2.1.4.** Non-ionizing radiation
  - **1.2.1.5.** UV radiation
  - **1.2.1.6.** Hypergravity
  - **1.2.1.7.** Hyperbaric conditions
  - **1.2.1.8.** Hypercapnia and hypoxia
  - **1.2.1.9.** Mechanical stretching
- **1.2.2.** Chemical-nutritional hormetins
  - **1.2.2.1.** Phytohormetins
  - **1.2.2.2.** Pro-oxidants
  - **1.2.2.3.** Nutritional micronutrients
  - **1.2.2.4.** Nutritional levels (food restriction)
- **1.2.3.** Psychological hormetins
  - **1.2.3.1.** Focussed attention and meditation

A.2. MAIN ISSUES TO BE RESOLVED

2.1. establishing molecular criteria for identifying hormetic effects of different stresses

2.2. establishing stress exposure regimens in terms of the intensity and frequency

2.3. identifying qualitative and quantitative differences in stress response pathways initiated by different stressors

2.4. determining the interactive and pleiotropic effects of multiple stresses

2.5. adjusting the levels of mild stress for age-related changes in the sensitivity to stress

2.6. determining the biological and evolutionary costs of repeated exposure to stress.

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Molecular mechanisms of hormesis
- **3.1.1.** Immediate signaling pathways: stress kinases
- **3.1.2.** Immediate stress responses and effector proteins
  - **3.1.2.1.** Heat shock proteins (hsp)
  - **3.1.2.2.** Nrf2 antioxidant response
  - **3.1.2.3.** DNA repair response
  - **3.1.2.3.** NFkB response
  - **3.1.2.4.** Unfolded protein response UPR
- **3.1.3.** Delayed stress responses and effector proteins
  - **3.1.3.1.** Antioxidant protection
    - **3.1.3.1.1.** Glutathione-peroxidase
    - **3.1.3.1.2.** Catalase
    - **3.1.3.1.3.** Superoxide dismutase
    - **3.1.3.1.4.** Methionine-reductase
    - **3.1.3.1.5.** Acetylases and deacetylases
  - **3.1.3.2.** DNA repair
    - **3.1.3.2.1.** Excision repair
    - **3.1.3.2.2.** Homologous recombination
    - **3.1.3.2.3.** Non-homologous end joining (NHEJ)
    - **3.1.3.2.4.** Mismatch repair
    - **3.1.3.2.5.** Post-replicative repair
  - **3.1.3.3.** Damaged protein proteolysis
    - **3.1.3.3.1.** Mitochondrial LON protease
    - **3.1.3.3.2.** Proteasome
    - **3.1.3.3.3.** Lysosomal proteolysis
  - **3.1.5.4.** Heat shock proteins and chaperones
    - **3.1.3.4.1.** Large hsp
    - **3.1.3.4.2.** Small hsp

3.2. Cellular mechanisms of hormesis
- **3.2.1.** Global changes in gene expression
- **3.2.2.** Global changes in epigenome
- **3.2.3.** Global changes in metabolome profile
- **3.2.4.** Intracellular structural alterations
- **3.2.5.** Global changes in secretosome profile
- **3.2.6.** Cell-cell interaction and communication

3.3. Tissue, organ and organismic level mechanisms of hormesis

3.3.1. Elimination of hypersensitive cell clones through apoptosis
3.3.2. Adaptive effect of some cells upon others - "bystander effect"
3.3.3. Antinflammatory responses
3.3.4. Stimulation of neuroendocrine stress responses

3.4. Multiple hormetins, cell type specificity and evolutionary costs
3.4.1. Effects of single and multiple hormetic challenges
3.4.2. Dose and timing of hormetic exposures
3.4.3. Cell specificity to single and multiple hormetins
3.4.4. Cost-benefit analysis in evolutionary and epidemiological terms, including population dynamics.

3.5. Mathematical modeling
3.5.1. Immediate and delayed hormesis
3.5.2. Network disruption and restabilisation with single and multiple hormetins
3.5.2 Predictions of the balance between the destructive and stimulating effects of hormetins

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. DEVELOPING NOVEL PHYSICAL HORMETINS

1.1. Thermal hormetic chambers
1.2. Hand-held thermal and radiation-based hormetic applicators
1.3. Hormetically designed exercise equipment
1.4. Scientifcally-operated spa and health-care treatments

B.2. DEVELOPING CHEMICAL AND NUTRITIONAL HORMETINS

2.1. Hormetic functional foods
2.2. Natural neutriceutical hormetins from plants
2.3. Natural neutriceutical hormetins from animals
2.4. Synthetic neutriceuticals
2.5. Hormetic mimetics of food restriction
2.6. Organ-specific natural and synthetic hormetins
2.7. Multi-hormetin pills and other formulations

B.3. DEVELOPING MENTAL AND PSYCHOLOGICAL HORMETINS

3.1. Novel brain hormetic tools and gadgets.
3.2. Hormetic protocols for meditation
3.3. Hormetic feel-good products, including cosmetics

Section **6**

CANCER AND AGING

THE INCIDENCE AND FREQUENCY OF CANCER increase progressively with age, but different organs and tissues show different patterns of age-related distribution of tumours. The susceptibility to initiation of carcinogenesis, and its rate and extent of promotion and progression also vary widely during aging. A number of physiological, immunological, cellular and molecular events, including mutations, influence the origin and expansion of cancer. Genetic factors, lifestyle influences, and stochastic events determine the incidence and consequences of cancer on health and longevity.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Cancer as a multi-hit genomic damage phenomenon

1.2. Linking cancer and aging:

- **1.2.1.** Escape from the Hayflick limit
- **1.2.2.** Maintenance of telomere length – either by telomerase activation or alternative to telomere (ALT) pathway)
  - **1.2.2.1.** hTERT
  - **1.2.2.2.** TRF2
- **1.2.3.** Inactivation of tumour suppressor genes
- **1.2.4.** p53, ARF, CARF
- **1.2.5.** CDKN2a (cyclin dependent kinases)
- **1.2.6.** RB1 (retinoblastoma 1)
- **1.2.7.** DNA-damage repair pathway components:
  - **1.2.7.1.** ATM (DSB repair)
  - **1.2.7.2.** XP family (NER)
  - **1.2.7.3.** RecQ family of DNA helicases (WRN, BLM, etc)
- **1.2.8.** Genomic instability links between cancer and aging
  - **1.2.8.1.** Marked loss of heterozygosity (LOH) in the daughter cell
  - **1.2.8.2.** Accumulation of somatic mutations
  - **1.2.8.3.** Stochastic variation in gene expression
  - **1.2.8.4.** Loss of maintenance from the Sirtuin pathway
  - **1.2.8.5.** Altered IGF-1 signaling

1.3. Link between cancer and aging also revealed via the study of some human genetic disease like:

- **1.3.1.** Ataxia–telangiectasia (A-T, ATM mutation)
- **1.3.2.** Xeroderma pigmentosum (XP gene mutation)
- **1.3.3.** Werner's syndrome (WRN mutation)
- **1.3.4.** Li-Fraumeni syndrome
- **1.3.5.** Breast Cancer (BRCA1)

1.4. Autophagy and cell biology of waste management links cancer and aging

- **1.4.1.** Beclin-1 (Becn-1) an autophagy gene binds to human oncogene B-cell CLL/lymphoma 2 (BCL2)
- **1.4.2.** Autophagy related genes – deletion linked to shortened lifespan
  - **1.4.2.1.** Atg5
  - **1.4.2.2.** Atg7
  - **1.4.2.3.** Daf-2

1.5. Inhibition of TOR (Target of Rapamycin) signaling

1.6. Analysis of a paraganglioma, a rare tumor that occurs in the carotid body, has linked metabolism, cancer and aging

- **1.6.1.** Mutations in essential enzymes of the metabolic pathways such as Krebs Cycle
  - **1.6.1.1.** Succinate dehydrogenase (SDH)
  - **1.6.1.2.** Fumarate hydratase
- **1.6.2.** Inhibition of the prolyl hydroxylase enzyme family
  - **1.6.2.1.** Degradation of hypoxia inducible factor 1 alpha (HIF1-α)
- **1.6.3.** Mutations in essential components of the Electron Transport Chain (ETC)

1.7. Discovery of epigenetic modulation linking cancer and aging

- **1.7.1.** Methylation
- **1.7.2.** Acetylation
- **1.7.3.** Histone modifications

A.2. MAIN ISSUES TO BE RESOLVED

2.1. Are cancers and aging two sides of the same coin?

2.2. Is it DNA damage itself or the response to DNA damage that kick starts aging and cancer?

2.3. Are the molecular regulatory systems involved in cancer networked with those in aging?

2.4. What are the common carcinogenic factors that are also age-related?

2.5. Are cancer and aging stem cell diseases?

2.6. Can systems biology approaches enhance our understanding of the molecular mechanisms behind the connections of many cancer and aging partners such as – p53, mTOR, FOXO proteins, HIF-1α etc.?

2.7. Can we elucidate the epigenetic mechanisms linking cancer and aging?

2.8. Can we identify markers and essential post-translational modifications that kick start aging and/or cancer?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Lifespan and unprompted tumor occurrence: evolutional aspect

- **3.1.1.** Species lifespan and cancer
- **3.1.2.** Lifespan diversity in different lines of the same species and cancer
- **3.1.3.** Population lifespan and cancer
- **3.1.4.** Species related traits of aging and carcinogenesis: mouse versus man?
- **3.1.5.** Age-related rise in human cancer incidence in different populations:
  - **3.1.5.1.** Malignant tumor occurrence in total
  - **3.1.5.2.** Colon and rectal cancers
  - **3.1.5.3.** Lung cancer
  - **3.1.5.4.** Endometrial cancer
  - **3.1.5.5.** Cervical cancer
  - **3.1.5.6.** Stomach cancer
  - **3.1.5.7.** Nephroncuses
  - **3.1.5.8.** Retinoblastoma
  - **3.1.5.9.** Liver tumors
  - **3.1.5.10.** Hemoblastosis
  - **3.1.5.11.** Skin cancer
  - **3.1.5.12.** Melanoblastoma
  - **3.1.5.13.** Encephaloma and neuroma
  - **3.1.5.14.** Benign tumors
- **3.1.6.** Age-related increase in unprompted tumor occurrence in model systems
  - **3.1.6.1.** Mouse tumors
  - **3.1.6.2.** Rat tumors
  - **3.1.6.3.** Hamster tumors
  - **3.1.6.4.** Cat tumors
  - **3.1.6.5.** Dog tumors
  - **3.1.6.6.** Farm animal tumors
- **3.1.7.** Unprompted tumor incidence reduction in most advanced age
  - **3.1.7.1.** Man
  - **3.1.7.2.** Rat
  - **3.1.7.3.** Mouse

3.2. Carcinogenic susceptibility in various ages

- **3.2.1.** Chemo-carcinogenesis and aging:
  - **3.2.1.1.** Skin
  - **3.2.1.2.** Soft tissues
  - **3.2.1.3.** Mammary gland
  - **3.2.1.4.** Liver
  - **3.2.1.5.** Digestive tract
  - **3.2.1.6.** Kidneys
  - **3.2.1.7.** Urinary bladder
  - **3.2.1.8.** Uterus and vagina
  - **3.2.1.9.** Lungs
  - **3.2.1.10.** Vascular walls
  - **3.2.1.11.** Hematopoietic system
  - **3.2.1.12.** Sinus
  - **3.2.1.13.** *In vitro* interventions
- **3.2.2.** Plastic carcinogenesis and aging
- **3.2.3.** Ionizing radiation and aging
  - **3.2.3.1.** Hematopoietic system
  - **3.2.3.2.** Ovaries
  - **3.2.3.3.** Mammary gland
  - **3.2.3.4.** Bones
  - **3.2.3.5.** Skin
  - **3.2.3.6.** Lungs
  - **3.2.3.7.** Thyroid gland
- **3.2.4.** Ultraviolet irradiation and aging
- **3.2.5.** Light regime, cancer and aging
  - **3.2.5.1.** Mammary gland
  - **3.2.5.2.** Digestive tract
  - **3.2.5.3.** Prostate gland
  - **3.2.5.4.** Uterus
  - **3.2.5.5.** Clock genes and cancer
  - **3.2.5.6.** Melatonin and cancer
- **3.2.6.** ELF electromagnetic field
  - **3.2.6.1.** Epidemiologic data
  - **3.2.6.2.** Animal testing observation data
- **3.2.7.** Hormonal carcinogenesis and aging
  - **3.2.7.1.** Estrogens
  - **3.2.7.2.** Progestins
  - **3.2.7.3.** Androgens
  - **3.2.7.4.** Growth hormone
  - **3.2.7.5.** Glucocorticoids
- **3.2.8.** Viral carcinogenesis and aging
  - **3.2.8.1.** Oncornaviruses
  - **3.2.8.2.** DNA-viruses

3.3. Age related carcinogenesis modification mechanisms

- **3.3.1.** Aging and multi-stage carcinogenesis model

3.3.2. Carcinogenesis model factor role
- **3.3.2.1.** Carcinogen type (direct and indirect action)
- **3.3.2.2.** Administration mode
- **3.3.2.3.** Exposure time (single, course, chronic)
- **3.3.2.4.** Exposure age
- **3.3.2.5.** Protocol pattern
- **3.3.2.6.** Statistical analysis

3.3.3. Pharmacodynamics of carcinogens and aging

3.3.4. Carcinogen metabolizing enzyme activity and aging
- **3.3.4.1.** 1st phase enzymes
- **3.3.4.2.** Monooxigenase system
- **3.3.4.3.** 2nd phase enzymes
- **3.3.4.4.** Mutagenicity test: effects of age

3.3.5. Carcinogen-macromolecule interaction in various ages

3.3.6. DNA repair, aging and carcinogenesis
- **3.3.6.1.** Types of DNA damage induced by carcinogens
- **3.3.6.2.** Age-related changes in DNA repair
- **3.3.6.3.** Age effect on DNA repair strength
- **3.3.6.4.** Aging in vitro and DNA repair
- **3.3.6.5.** Progeria and DNA repair

3.3.7. Age-related mutations and other macromolecule damage accumulation in various tissues and organs

3.4. Carcinogenesis promotion factors and aging

3.4.1. Growth factors, aging and cancer

3.4.2. Age-related nervous system alterations and cancer

3.4.3. Age-related lipid-carbohydrate metabolism alterations and cancer

3.4.4. Age-related immune system alterations and cancer

3.4.5. Transplantable tumor expansion in various ages

3.4.6. Tumor expansion rate, prognosis and survivability of cancer patients at various ages

3.5. Carcinogenic aging

3.5.1. Carcinogen impact on lifespan

3.5.2. Carcinogen impact on nervous system

3.5.3. Carcinogen impact on endocrine system

3.5.4. Carcinogen impact on lipid-carbohydrate metabolism

3.5.5. Carcinogen impact on immune system

3.5.5.1. Mice with reproductive system accelerated aging.

3.5.5.2. Circadian cycle gene mutations

3.5.6. Genetic mutations delaying aging in mice

3.5.7. Cloned from somatic cells mice life span

3.6. Life extension and cancer risk

3.6.1. Caloric restriction and oncogenesis
- **3.6.1.1.** Diet and human cancer
- **3.6.1.2.** Non-human primates
- **3.6.1.3.** Rats
- **3.6.1.4.** Mice

3.6.2. Life extension drugs and tumor progression risk
- **3.6.2.1.** Antloxidants
- **3.6.2.2.** Ethanol and resveratrol
- **3.6.2.3.** Cross-linking inhibitors
- **3.6.2.4.** Neurotropic drugs
- **3.6.2.5.** Adaptogenes
- **3.6.2.6.** Succinic acid
- **3.6.2.7.** Thyroid body hormones
- **3.6.2.8.** Corticosteroids and DHEA
- **3.6.2.9.** Estrogens and hormonal contraceptives
- **3.6.2.10.** Growth hormone
- **3.6.2.11.** Anti-diabetic drugs
- **3.6.2.12.** Melatonin
- **3.6.2.13.** Peptide bioregulators
- **3.6.2.14.** Immunomodulators
- **3.6.2.15.** Enterosorbents
- **3.6.2.16.** Other drugs

3.6.3. Stem cells, aging and cancer

3.6.4. Physical exercises and cancer
- **3.6.4.1.** Epidemiologic data
- **3.6.4.2.** Experimental data

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. PERSONALIZED GENOMICS

1.1. Early-stage cancer detection kits

1.2. Counselling market to explain cancer and aging risk

1.3. Regulatory market development in the area of anti-cancer compounds

B.2. MOLECULAR/GENETIC INTERVENTIONS TO PREDICT DISEASE AND TAKE PRE-EMPTIVE MEASURES

B.3. TESTTING NOVEL SYNTHETIC AND NATURAL COMPOUNDS FOR ANTI-CANCER PROPERTIES

B.3. DEVELOPMENT OF MOUSE MODELS OF CANCER AND AGING

B.4. CARCINOGEN MARKET

4.1. Identification of carcinogens in natural and synthetic materials

4.2. Legal issues of handling of carcinogens

4.3. Testing of Carcinogen effects for industry and private applications

Section **7**

METABOLOME AND METABOLIC ASPECTS OF AGING AND LONGEVITY

THE GENETIC INSTRUCTIONS CODED in the nucleic acids become eventually meaningful in a structural and functional sense in the form of hundreds of thousands of metabolites within a cell. The importance and complexity of the metabolism and its components comprising the so-called metabolome is only beginning to be unravelled in the context of aging and longevity. Metabolomics promises to be the future central theme of aging research and interventions.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Age-dependent changes in various metabolic processes

- **1.1.1.** DNA replication and bulk transcription
- **1.1.2.** Individual RNA synthesis
- **1.1.3.** Bulk protein synthesis and degradation
- **1.1.4.** Individual protein synthesis, activities, amounts and degradation
- **1.1.5.** Carbohydrate metabolism
- **1.1.6.** Fatty acid metabolismIncreased knowledge of cellular bioenergentics:
- **1.1.7.** Mitochondrial metabolism
  - **1.1.7.1.** Electron transport chain and ATP generation
  - **1.1.7.2.** Calcium homeostasis
  - **1.1.7.3.** ROS generation
  - **1.1.7.4.** Apoptosis induction
- **1.1.8.** Oxidation
- **1.1.9.** Glycolysis
- **1.1.10.** Phosphorylation

1.2. Physiological changes as a function of age

- **1.2.1.** Water imbalance
- **1.2.2.** Hormones
- **1.2.3.** Neurotransmitters
- **1.2.4.** Insulin resistance and glucose metabolism

A.2. MAIN ISSUES TO BE RESOLVED

2.1. What is the relationship between metabolic rates and longevity?

2.2. What are the metabolite profiles for various metabolic processes in different cells, tissues, and organs as a function of age?

2.3. What is the range of healthy and diseased profiles of a specific or a group of metabolites?

2.4. Can controlling metabolic effects and metabolites modulate lifespan?

2.5. What is the association between age-associated energy substrate metabolism changes and age related pathologies?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Investigating reduced oxygen consumption with age

- **3.1.1.** Study of oxygen consumption at the cellular level
  - **3.1.1.1.** Analysis of structural and functional changes in mitochondria:
    - **3.1.1.1.1.** Alterations of mitochondrial genome
    - **3.1.1.1.2.** Alterations of the respiratory chain
    - **3.1.1.1.3.** Changes related to cell nucleus
    - **3.1.1.1.4.** Proliferation of mitochondria
  - **3.1.1.2.** Study of extramitochondrial oxidation:
    - **3.1.1.2.1.** Peroxysoms, their formation and functions
    - **3.1.1.2.2.** Cytoplasmic oxidases
    - **3.1.1.2.3.** The regulation system of antioxidant protection
    - **3.1.1.2.4.** Active oxygen species as an additional energy source
  - **3.1.1.3.** Proliferation of mitochondria
  - **3.1.1.4.** Protein (carbonylation)
  - **3.1.1.5.** Lipids (malondialdehyde and 4-hydroxynonenal)
- **3.1.2.** Study of oxygen consumption at the organism level:
  - **3.1.2.1.** Development of methods to assess the degree of tissue oxygenation at rest and during physical activity
  - **3.1.2.2.** Development of methods to assess the level of consumption of energy substrates at rest and during physical activity
  - **3.1.2.3.** Determination of physical stress age limit

3.2. Investigation of aging as adaptation to the changes in the organism's internal environment

- **3.2.1.** Studying the age-dependant oxidative stress
  - **3.2.1.1.** Lipotoxicity as the consequence of fatty acids homeostasis failure
    - **3.2.1.1.1.** Lipofuscin synthesis
    - **3.2.1.1.2.** Protein synthesis reduction
    - **3.2.1.1.3.** Apoptosis
    - **3.2.1.1.4.** Cell dedifferentiation
    - **3.2.1.1.5.** Differentiation as an adipose-related phenotype.
  - **3.2.1.2.** Glucosetoxicity as the consequence of glucose homeostasis failure:
    - **3.2.1.2.1.** Extracellular proteins glycosilation
    - **3.2.1.2.2.** Skin aging
    - **3.2.1.2.3.** Lens aging
    - **3.2.1.2.4.** Neuron apoptosis
    - **3.2.1.2.5.** Amyloidosis
- **3.2.2.** Age-related hypercholesterolemia:
  - **3.2.2.1.** Cytoplasm membrane structure changes

3.2.2.2. Raft structure and function alterations

3.2.2.3. Receptor sensitivity decrease

3.2.3. Age-related and alimentary hyperhomolocysteinemia:

3.2.3.1. Impact on specific receptors in the neural and immune systems

3.2.3.2. Toxicity mechanisms

3.2.3.3. Compensatory methods

3.3. Investigation of age-related changes in energy substrates expenditure (glucose and fatty acids):

3.3.1. Research of glucose and fatty acid distribution mechanisms in the organism:

3.3.1.1. Investigation of glucose and fatty acids homeostasis support system and causes of its age-related failure

3.3.1.2. Study of relationship between metabolic and gene networks

3.3.1.3. Study of the role of metabolites as regulators of gene expression

3.3.1.4. Identification of genes responsible for glucose and fatty acid homeostasis support and their influence on longevity

3.3.2. Exploring the causes of age-dependent fat amount increase in humans:

3.3.2.1. Studying the role of fatty acids in proliferation, differentiation and apoptosis

3.3.2.2. Structure-functional analysis of changes in adipose tissue

3.3.2.3. Studying the "Metabolic knot" functioning (adipose tissue, muscle, liver) and its changes in ontogenesis

3.3.2.4. Studying the mechanisms of age-related fatty transformation of non-adipose tissues

3.4. Studying the relation between age-associated energy substrate metabolism changes and age-related pathologies development

3.4.1. Atherosclerosis

3.4.2. Arterial hypertension

3.4.3. Insulin-independent diabetes type 2

3.4.4. Intestine dysbacteriosis

3.4.5. Autoimmune diseases

3.4.6. Cancer

3.4.7. Neurodegenerative process

3.4.8. Osteoporosis

3.5. Investigation of age-dependent changes of substrate homeostasis

3.5.1. Investigation of the role of hypothalamus in collapse of fatty acids homeostasis- Investigation of age-dependent disorders in the APUD system

3.5.2. Study of age-related changes in functioning of adipose tissue as an endocrine organ.

3.5.3. Study of changes in the internal medium of the organism in the process of aging, its connection with hormonal disregulation

3.5.4. Study of the causes of age-related stress, its effects and adaptation mechanisms Investigating multiple parameters within the same model system

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. DEVELOPMENT OF A METABOLOME TO SUPPORT METABOLITE SCREENING AND GENERAL UNDERSTANDING OF METABOLIC FUNCTIONS IN AGING

1.1. Methods to identify important metabolites relevant to health and longevity

1.2. Diagnostic kits for changes in the levels of metabolites

1.3. "Nano-sensors" or implantable chips that can provide real-time data of oxygen rates, lipid profiles, cholesterol values etc.

B.2. NICHE MARKET TARGETING RESEARCHERS (ACADEMIC AND INDUSTRIAL) WITH NEW LAB TOOLS TO MEASURE METABOLITE RATES, METABOLITE TAGGING FOR "REAL-TIME" IMAGING IN CELLS, HIGH THROUGHPUT SCREENIN GOF DRUGS

2.1. Nano-oxygen meters

2.2. Lipid modification techniques and kits

2.3. Animal models specifically designed for metabolome studies

2.4. Creating novel cell lines for metabolic screening and interventional studies

Section **8**

IMMUNITY AND AGING

AGING OF THE IMMUNE SYSTEM or immunosenescnce is one of the most critical effectors of health, survival and longevity. Alterations in the structure and function of various components of the adaptive and innate immunity can be both the cause and the consequecne of aging and age-related diseases, including infections, heart failure, autoimmunity and cancer. Although constant remodelling of the immune system is a feature of adaptation, progressive shrinkage of the immunological space can be the rate limiting step for the quality and duration of life.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Overall decline in the function of the immune system during aging

1.2. Thymic involution and atrophy

1.3. Age-dependent alterations in immune system cells

1.3.1. Increase in the ratio of memory to naive T cells

1.3.2. Decrease in the number of B cells

1.3.3. Increased levels of autoantibodies

1.3.4. Alterations in cytokines

A.2. MAIN ISSUES TO BE RESOLVED

2.1. What is the correlation between altered cell numbers and immunological efficiency?

2.2. What is the significance of reduced antibody repertoire during aging?

2.3. What is the role of age-related decrease in humoral immunity in protection against bacteria and viruses?

2.4. What are the genetic regulators of immunity during aging?

2.5. What is the role of autoimmunity in health and disease during aging?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1.1. Interaction between aging and function of the immune system organs

3.1.1.1. Central and peripheral immunogenic organs

3.1.1.2. Thymus involution

3.1.1.3. Bone marrow

3.1.1.4. Lymphoepithelial masses

3.1.1.5. Lymph nodes

3.1.2. Changes in immune privileged organs and tissues

3.1.2.1. Central nervous system (CNS)

3.1.2.2. Testicles

3.1.2.3. Eyes

3.1.2.4. Thymus parenchyma

3.1.3. Cell immunity as the main factor of body protection against viruses, pathogenic fungi, intracellular bacteria, tumors.

3.1.4. Morphofunctional and phenotypic features of immunity effectors during aging

3.1.5. Change in the quantity and correlation of immunocompetent cells

3.1.6. Correlation of mononuclear and polymorphonuclear leukocytes

3.1.7. chemotaxis and chemokines production

3.1.8. Neutrophil generation and function

3.1.9. intencivity of ''oxygen explosion'' processes

3.1.10. expression conglutination molecules and TREM-(triggering receptor expressed on myeloid cell-1

3.1.11. Lymphocyte functional disorder

3.1.12. Th1/ Th2 lymphosytes disballance

3.1.13. phagocytic activity of neutrophils and macrophages

3.1.14. dendritic cell generation and cytokine production

3.1.15. T / B cell ratio

3.1.16. CB4+/CB8+ cell ratio

3.1.17. NK and NKT cells content

3.1.18. T-regulatory cells (suppressors) (CD4+CD25+Foxp3+)

3.1.19. T-helper clone formation

3.1.20. expression of molecules of antigenic presentation and co-stimulating molecules

3.1.21. expression of pattern-recognizing receptors

3.1.22. expression on dendritic cells markers of terminal differentiation

3.2. Investigation of humoral immunity playing the main role in protecting the body against bacteria present in intracellular space and blood.

3.2.1. Functioning mechanisms of antibodies of different classes and subclasses during aging

3.2.2. Possibility of restoring immune response as a trend in prophylaxis of age-related diseases.

3.2.3. Study of immunoglobulin disbalance mechanismin in aging

3.2.4. Correlation of the content of memory B-cells and concentration of serum immunoglobulins

3.2.5. Change of repertoire and variety of antibodies secreted by B-cells

3.2.6. Mucosal immunity evaluation

3.3. Investigation of genetic regulation of immunoreactivity

3.4. Immunological aging biomarkers

3.4.1.1. Identification of the immune risk phenotype

3.4.1.2. Disorders of the phenotype and function of congenital and acquired immunity effectors

3.4.1.3. The specificity of cytokine profile

3.4.1.4. Autoimmune reactions

3.4.1.5. Development of a chronic inflammatory reaction

3.4.1.6. Identification of the immuno-inflammatory status (inflamm-aging status) signs

3.4.1.7. Markers' expression and functional NK activity

3.4.1.8. Phenotypical specificity of cytotoxic lymphocytes

3.4.1.9. Establishment of the level of anti-inflammatory cytokines and pathogen-associated complexes in blood

3.4.1.10. Assessment of translocation of bacteria and microbe-associated complexes (ligands of Toll-like receptors) from intestine

3.5. Reconstruction of the body immune homeostasis (immunorehabilitation) during aging

3.6. Obtaining transgenic animals with expression of autoreactive T-cell receptors

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. DEVELOPMENT OF SINGLE OR MULTI-COMPONENT IMMUNOSTIMULANT NUTRICEUTICALS

B.2. DEVELOPMENT OF NATURAL AND SYNTHETIC SPECIFIC INHIBITORS OF AUTOIMMUNITY

B.3. DIAGNOSTIC KITS FOR IMMUNO-STATUS PROFILE

B.4. DEVELOPMENT OF NOVEL ANTI-INFLAMMATORY DRUGS

B.5. GENETIC ASSOCIATIONS AND DEVELOMENT OF PERSONALISED IMMUNE MODULATORS

Section **9**

ENDOCRINOLOGIC ASPECTS OF AGING

THE ENDOCRINE SYSTEM, including the autocrine and paracrine hormonal glands and other sites of hormone production, has been considered as the master regulator of growth, development, reproduction and aging. An age-related decline in the levels of various hormones has been the basis for numerous so-called anti-aging and rejuvenating therapies. However, recent research shows that a decline in hormonal levels may actually be a sign of body's adaptive response for survival, and any simplistic attempts to restore the hormonal levels in old age to those of young age may even be detrimental for aging and longevity.

(A) BASIC RESEARCH ASPECTS

A.1. ALREADY ESTABLISHED FACTS

1.1. Almost all components of the endocrine system undergo changes with aging, and these changes occur independent of age-related disorders/diseases

1.2. Endocrine functions are reduced with age due to either a reduction in the production and secretion of hormones or a reduction in the sensitivity of hormone receptors

1.3. External factors like metals, medicines and xenobiotics have an effect on the endocrine system in accelerating aging

1.4. In the absence of serious hormonal deficiency and disorder, hormone replacement therapy can have adverse side effects

A.2. MAIN ISSUES TO BE RESOLVED

2.1. What is the correlation between age-related malfunction of hormone production, signs of aging and the progression of age-related diseases?

2.2. What are the normal and target values of blood hormones in substitutive hormone therapy?

2.3. What are the metabolic side effects of hormones and medicines for chronic diseases?

2.4. What are the neuro-endocrine interactions with respect to changing hormone levels during aging?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Mechanisms of age-related alterations and regulation of endocrine organs

3.1.1. Study of the key organs in the endocrine system in context to age-related alterations

3.1.1.1. Hypothalamus, the key organ coordinating the entire endocrine system activity

3.1.1.1.1. Structural and functional alterations of superchiasmatic hypothalamic nuclei which play a major role in generation of circadian rythms of endocrine glands

3.1.1.1.2. Abnormality in the afferent impact of retinohypothalamic system, hippocampus; alteration of the blood-brain barrier penetrability for various effectors perceived by the hypothalamus

3.1.1.1.3. Abnormal perfusion of hypothalamus and areas responsible for afferent effects

3.1.1.1.4. Decrease of dopaminergic tonus

3.1.1.2. Epiphysis

3.1.1.2.1. Age-related morphological alteration of epiphysis

3.1.1.2.2. Regulation of melatonin and other epiphysis generated peptides

3.1.1.2.3. Study of the species-related differences in the diurnal melatonin production rhythm and its susceptibility to environmental load (for example, light "pollutants")

3.1.1.3. Pituitary gland

3.1.1.3.1. Structural and functional alterations of the prepituitary gland

3.1.1.3.2. Structural and functional alteration of the posterior pituitary gland

3.1.1.3.3. Hypothalamus control response distortion

3.1.1.3.4. Decrease of the epiphysis control response

3.1.1.3.5. Role of hypophysis vascular malformation

3.1.1.3.6. Autoimmune destruction of pituitary gland

3.1.2. Study of the peripheral organs of endocrine system

3.1.2.1. Islets of Langerhans of pancreatic beta-cells

3.1.2.2. Ovaries

3.1.2.3. Testicles

3.1.2.4. Thyroid gland

3.1.2.5. Adrenal glands

3.1.2.6. Adipose tissue

3.1.2.7. APUD system cells

3.2. Immune mechanisms of endocrine gland damage in the aged

3.2.1. Age-related prevalence of organo-specific autoantibodies

3.2.2. Impact of organo-specific autoantibodies on endocrine gland functioning

3.2.3. Organo-specific antigen identification

3.2.4. Formation of antibody-hormone complexes to decrease biological activity of hormones and their metabolism (macroprolactinemia, etc.)

3.2.5. Evaluation of cytokine profile and inflammation markers and their influence on endocrine gland functioning

3.3. Genetic control mechanisms and regulation of the endocrinal function in the aged

3.3.1. Endocrine receptor complexes and effector tissue alterations in the process of aging

3.3.1.1. Study of hormone receptor gene polymorphism influence on the sensitivity and density of receptors in tissues.

3.3.1.2. Search for indirect estimate markers of hormone receptors functional activity

3.4. Impact of intracellular signalling pathways on lifespan

3.4.1. Endogenic ligands, functional activity of LXR nuclear receptors and their influence on human lifespan extension (as compared to the existing data on C. elegance, D. melanogaster)

3.4.2. Role of sirtuins in the development of various diseases,

3.4.3. Role of insulin and insulin receptor, insulin resistance, growth hormone, IGF-1, and receptors to them (IGF-1R, GHR), postreceptor pathways (IRS1 and IRS2, etc.)

3.5. Involvement of mitochondria in the aging of endocrine glands

3.6. Study of the impact of substitutive therapy on the secretory regulation of other hormones

3.7. Safety assessment of hormone therapy

3.8. Identification of the pattern for secretion and hormone metabolism in the aged

3.8.1. Hormone levels that give protection against the development of age-related diseases

3.8.2. Distortion of hormone secretion rhythm in old age

3.9. Biological activity of the synthesized hormones

3.9.1. Polymerization

3.9.2. Binding to blood proteins

3.9.3. Formation of inactive complexes with antibodies

3.9.4. Interaction with receptors

3.10. Post-secretory metabolism of hormones

3.11. Identification of exogenic factors responsible for the the incretory glands malfunction and examination of their modes of action

3.11.1. Nutrients deficiency: avitaminosis and microelement deficiency

3.11.2. Endocrine disruptors: thyocyanates, isoflavons, disulfides, chlorine-containing organic substances, including synthetic pesticides and insecticides

3.11.3. Influence of environmental stress and exogenic glucocorticoid hormones during infanthood

3.12. Determination of mechanisms of hormonal carcinogenesis

3.12.1. Identification of hormone-sensitive tumorigenesis

3.12.2. Study of location of hormone receptors on tumor cells and their functional activity

3.12.3. Mechanisms of influence of hormones on the growth rate and mitosis of tumor cells

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. NOVEL APPROACHES FOR THE RESTORATION OF ENDOCRINE GLAND FUNCTION

1.1. Beta-cells planting

1.2. Development of pharmacological means of stimulation of mechanisms that increase the amount of endogenous beta-cells

1.3. Gene therapy of endocrine diseases

1.4. Development of medicine to enhance sensitivity of hypothalamus to the homeostatic stimuli

B.2. FORMULATION OF PROTOCOLS FOR SUBSTITUTIVE HORMONE THERAPY FOR THE IDENTIFIED MALFUNCTION OF ENDOCRINE GLANDS

B.3. SUBSTITUTIVE HORMONE THERAPY THROUGH PHARMA-, NUTRI- AND COSME-CEUTICALS CONTAINING:

3.1. Melatonin

3.2. Somatotropin

3.3. Secretion products of growth hormone, such as somatoliberin, ghrelin and agonists of ghrelin

3.4. Tiroxin

3.6. Glucocorticoids

3.7. Mineralocorticoids

3.8. Androgens

3.9. Chorionic gonadotropin

3.10. Menotropin

3.11. Estrogen

3.12. Gestagen

3.13. Dehydroepiandrosteron and dehydroapiandrosteron sulfate

3.14. Insulin

3.15. Amylin

3.16. Erythropoetin

B.4. NON-HORMONAL INTERVENTIONS FOR IMPAIRED ENDOCRINE-RELATED FUNCTIONING

4.1. Dislipoproteinemia

4.2. Decrease in mineral density of bone tissue

4.2.1. Antiresorptive preparations (bis-phosponates)

4.2.2. Selective modulators of estogenic receptors (SERM)

4.2.3. Bone-anabolic preparations (analogues of parathormone and simvastatin)

4.3. Carbohydrate metabolism - metformin

4.4. Hypertension

4.5. Rationalization of polypharmaceutical therapy

4.5.1. Safer analogs for metabolically unfavorable drugs substitution

4.5.2. Identification of versatile pharmacotherapy medication

Section **10**

EPIGENETICS OF AGING AND AGE-RELATED DISORDERS

EPIGENETICS IS THE ENCODING and inheritance of information without involving any changes in the base sequence in DNA. This includes all those mechanisms necessary to unfold the genetic programme for development, growth and maturation, such as DNA methylation, histone modifications, alternative transcript splicing, small RNAs, noncoding RNAs and gene silencing. Epigenetic heritable changes are known as epimutations, and various factors, including lifestyle and diet affect the rate and extent of aging and the occurrence and emergence of various age-related disorders, including Alzheimer's disease, cancer and osteoarthritis.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Age-related changes in bulk DNA methylation levels

1.2. Age-dependent remodeling of chromatin

- **1.2.1.** Histone modifications (acetylation, methylation, phosphorylation)
- **1.2.2.** Dynamic reorganization of the heterochromatin
- **1.2.3.** Formation of specialized sections of the facultative heterochromatin
- **1.2.4.** Reorganisation of the heterochromatin in premature accelerated aging
- **1.2.5.** Polycomb (PcG) and Trithorax (trxG) proteins and their functional human counterparts in epigenetic regulation

A.2. MAIN ISSUES TO BE RESOLVED

2.1. Are bulk changes in DNA methylation cell- and tissue-specific ?

2.2. Are there gene-specific changes in DNA methylation?

2.3. Are histone modifications during aging cell- and tissue-specific?

2.4. What are the age-related profiles of small and noncoding RNAs?

2.5. How does epigenetics regulate gene silencing and reactivation during aging?

2.6. What is the correlation between epigenetic modifications and cellular functionality?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

1.1. Impact of environmental factors on epigenetic processes during aging

- **1.1.1.** Heavy metals and micronutrients
- **1.1.2.** Bioactive food components, including vitamins
- **1.1.3.** Phytoestrogens
- **1.1.4.** Xenohormetic compounds and hormetins, including polyphenols and flavanoids
- **1.1.5.** Fatty acids and lipds
- **1.1.6.** Carbohydrates
- **1.1.7.** Proteins

1.2. Influence of lifestyle on epigenotype during aging

- **1.2.1.** Psycho-active substances (alcohol, nicotine, opiates, marijuana)
- **1.2.2.** Calorie restriction
- **1.2.3.** Physical activity
- **1.2.4.** Mental stress
- **1.2.5.** Impact of medical procedures on epigenotype during aging

1.3. Circadian epigenetic programming and its role in aging

1.4. Epigenetic variations in monozygotic twins during aging

1.5. Aging and resetting of the epigenotype while cloning

1.6. Epigenetic epidemiology of age-dependent disorders

- **1.6.1.** Pre- and post-natal epigenetic programming of age-dependent disorders
  - **1.6.1.1.** Metabolic syndrome
  - **1.6.1.2.** Hyperlipidemia
  - **1.6.1.3.** Hypertension
  - **1.6.1.4.** Insulin resistance
  - **1.6.1.5.** Autoimmune disorders
  - **1.6.1.6.** Neurodegereative disorders
  - **1.6.1.7.** Sarcopenia
  - **1.6.1.8.** Osteoporosis
  - **1.6.1.9.** Aterosclerosis
  - **1.6.1.10.** Cancers

1.7. Epigenetic processes using the models of nucleocytoplasmic hybrids

1.8. Epigenetic mechanisms of neonatal imprinting as a function of age

1.9. Epigenetic factors involved in the large offspring syndrome in cloning

1.10. Role of epigenetics in the Lansing effect – the effect of age of the parents

1.11. Epigenetic modifications in heterochronic the transplantations of stem cells (from old animals to young ones and vice versa

1.12. Epigenetic processes in reprogramming somatic cells into stem cells (induced pluripotency) during aging

1.13. Epigenetic processes in rejuvenating plants through deep pruning

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. DEVELOPMENT OF SINGLE OR MULTI-VARIABLE KITS TO DETERMINE THE EPIGENETIC STATUS IN BLOOD CELLS

B.2. PERSONAL USE SCREENING METHODS FOR NATURAL AND SYNTHETIC FOOD COMPONENTS FOR EPIGENETIC MODULATION

B.3. DEVELOPING MEDICATIONS THAT WILL TARGET SPECIFIC GROUPS OF GENES ASSOCIATED WITH LIFE EXPECTANCY BY MEANS OF INTRODUCING SPECIALIZED AGENTS (FOR INSTANCE, SMALL INTERFERING RNA) TO ARTIFICIALLY CREATE LONG LIVING PHENOTYPES

B.4. POSSIBILITY OF REACTIVATING THE HETEROCHROMATIN REGIONS OF THE CHROMOSOMES IN ELDERLY PEOPLE WITH THE HELP OF PEPTIDE BIOREGULATORS (INCLUDING VILON, EPITALON, KORTAGEN, LIVAGEN, PROSTAMAX)

B.5. POSSIBILITY OF EPIGENETICALLY REPROGRAMMING SOMATIC CELLS WITH THE HELP OF NUCLEAR AND CYTOPLASMIC EXTRACTS OBTAINED FROM PLURIPOTENT CELLS

B.6. THE DEVELOPMENT OF MEDICATIONS TO PREVENT AGE DEPENDENT DISORDERS (SUCH AS CANCERS) BY TARGETING THE AGE ASSOCIATED SECTIONS OF FACULTATIVE HETEROCHROMATIN (SAHF).

Section **11**

EPIDEMIOLOGY AND BIODEMOGRAPHY OF AGEING AND AGE-DEPENDENT DISORDERS

HUMAN AGEING IS BEING progressively slowed down and average longevity of the population is increasing. This has profound socio-economic implications for individuals, populations and society. Research by demographers, epidemiologists and other bigerontologists suggests that further progress will be made in extending both the lifespan and the health-span of an increasing number of individuals in all populations, thus decreasing the demographic load of frailty and dependence.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Global trends in biodemography

- **1.1.1.** Decreasing rates of mortality at all ages
- **1.1.2.** Flattening of the mortality curve at advanced ages

1.2. Global trends in epidemiology of various age-related diseases

- **1.2.1.** Metabolic syndrome
- **1.2.2.** Cardiovascular diseases
- **1.2.3.** Neurodegenerative diseases
- **1.2.4.** Musco-skeletal
- **1.2.5.** Visual impairments
- **1.2.6.** Cancers

1.3. Established risk factors for disease with linked epidemiological data

- **1.3.1.** Physical inactivity
- **1.3.2.** Stress
  - **1.3.2.1.** Physical
  - **1.3.2.2.** Emotional
  - **1.3.2.3.** Mental
- **1.3.3.** Alcohol consumption
- **1.3.4.** Obesity
- **1.3.5.** Hereditary (genetic)
- **1.3.6.** Environmental

1.4. Emergence of various bioinformatic analytic tools useful for biodeomgraphic and epidemiological studies

- **1.4.1.** NetAGE
- **1.4.2.** HAGR (Human Ageing Genomic Resource)
- **1.4.3.** GAN (Gene Aging Nexus)
- **1.4.4.** GenAge

A.2. MAIN ISSUES TO BE RESOLVED

2.1. What are the population-specific genetic markers for predisposition to various age-related diseases?

2.2. What are the population-based epidemiological profiles for major lifestyle diseases?

2.3. What is the range of rates of aging in different populations and individuals?

2.4. What are the theoretical limits to longevity extension?

2.5. What are the public health issues related to population longevity extension?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Establishing genome-wide association studies of the major age-related diseases

- **3.1.1.** Cardiovascular
- **3.1.2.** Neurodegenerative
- **3.1.3.** Metabolic syndrome
- **3.1.4.** Visual
- **3.1.5.** Muscular

3.2. Using bio-informatics analysis to identify the candidate genes that may be responsible for the predisposition to obesity and other symptoms of the metabolic syndrome in people of different ages

3.3. Epigenetic factors associated with increased predisposition to obesity and type 2 diabetes among some ethnic groups (Pima Indians, Australian aborigines, Ethiopian Jews)

3.4. Longevity factors in twins – assessment of genetic, environmental and biological factors

3.5. Identifying the associations between food influences (diet) and the genetic polymorphism in different populations with age-related disorders

- **3.5.1.** Determining the role of calcium and vitamin B consumption in insulin resistance and predisposition to type 2 diabetes in elderly people
- **3.5.2.** Estimating the influence of fiber products and fats in the food intake of large population as well as that of the glycemic index on the food parameters that characterize the metabolism and the body mass index in people
- **3.5.3.** Developing the principles of a healthy hypocaloric diet that follows modern dietary recommendations; long term observation (2 years and more) of the weight and fat loss trends in obese people who are following this diet
- **3.5.4.** Genetics behind the well established dogma of caloric restriction for longevity.

3.5.5. Changes in the body weight and other parameters that constitute risk factors for cardiovascular disorders

3.5.6. The influence of vitamin B11 and folacin consumption with food on the risk of developing Alzheimer's disease, cardiovascular disease etc.

3.5.7. Using epidemiological research to test whether it is possible to prevent or delay the development of age-related cataracts by enriching food with antioxidants and saturated fat acids

3.5.8. The effectiveness of using lutein and polyphenols contained in tea to prevent age-related central visual degeneration

3.5.9. Determining the ratio of proteins and nucleic acids in food that is optimal for the functioning of muscles and bones in elderly people

3.5.10. Influence of vitamin K on the density of bone tissue, determining endogenous and exogenous factors affecting the absorption and transport of vitamin K (the lipid profile, age, consumption of vitamin K with food) in elderly people;

3.6. Determining the associations between the status of vitamin B, consumption of metonine and homocysteine in the blood plasma with population specific gene polymorphisms

3.7. Assessment of lifestyle effects on genes and metabolism – combining surveys and biochemistry:

3.7.1. Smoking

3.7.2. Overeating

3.7.3. Excessive alcohol consumption

3.7.4. Excessive coffee consumption

3.7.5. Lack of physical activity

3.7.6. Lack of or excessive sleep

3.8. The role of hyperhomocysteinemia in

3.8.1. Age-related reduction of neural functions and cognitive abilities

3.8.2. Pathogenesis of micro vascular and thrombotic complications of cardiovascular disorders

3.9. Using epidemiological research to study the role of single carbon food components in the modification of the metabolic and genetic paths resulting in the development of cancerous cells:

3.9.1. methionine;

3.9.2. choline;

3.9.3. folate;

3.9.4. group B vitamins (including B2, B6 and B11);

3.9.5. Single group antagonists (including alcohol).

3.10. Determining the biochemical and pathophysiological processes that form the basis of the influence of vitamin D and calcium on carcinogenesis; studying the genetic and environmental factors influencing these effects

3.11. Epidemiology of cultural and population effects of long-lived individuals

3.12. Research on factors underlying areas of exceptional longevity:

3.12.1. Abkhazia

3.12.2. Andes

3.12.3. Altai

3.12.4. Yakutia

3.12.5. Okinawa

3.12.6. Sardinia

3.13. Making a detailed database of positive effects of established and newly identified, additives, food supplements and other positive modulators of human health

3.13.1. Vitamins and some of their positive effects

3.13.2. Anti-oxidants

3.13.3. Minerals

3.13.4. Catechols

3.13.5. Hormetins including polyphenols and flavonoids

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. PERSONALIZED/POPULATION BASED MEDICINE

1.1. Development of population-specific databases

1.2. Biomarker discovery to assess epidemiological factors in age-related disorders

1.3. Food supplements and additives market to promote healthy aging

B.2. MOLECULAR/GENETIC INTERVENTIONS TO PREDICT DISEASE AND TAKE PRE-EMPTIVE MEASURES

B.3. DEVELOPING AND TESTING WEB APPLICATIONS FOR THE CALCULATION OF OPTIMAL DIETS AND PHYSICAL ACTIVITY LEVELS TO PROMOTE HEALTH

Section **12**

MICROBIOLOGY AND AGING

MICROORGANISMS OR MICROBES that live internally and externally on our bodies comprise our microbiota. The specific habitat or niche these microbiota occupy is what comprises our microecology. While knowledge of specific microbes inhabiting certain niches within the human body has been known for some time now, their relative dynamics, fluctuating populations (owing to intrinsic competition induced by human habits, behavior and immune system), and their impact and relevance on human health, immune defense, disease resistance and aging is a relative new phenomenon yet to be fully elucidated. This complex relationship between microbiota and health, and its immediate and long term effects on human aging require urgent attention with respect to its relevance for anti-aging interventions.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Presence of resident microorganisms in distinct niches throughout the human body

- **1.1.1.** Bacteria
- **1.1.2.** Fungi
- **1.1.3.** Protozoans
- **1.1.4.** Viruses

1.2. Identified Niches

- **1.2.1.** Oral mucosa
- **1.2.2.** Skin surface
- **1.2.3.** Oro-pharyngeal tract
- **1.2.4.** Gastrointestinal tract
- **1.2.5.** Urogenital tract
- **1.2.6.** Rectum

1.3. Maintenance of "homeostasis" or balance of competing organisms (the good vs. bad bacteria balance)

- **1.3.1.** Opportunistic pathogens such as Candida albicans, Staphylococcus epidermidis normally kept in check by other commensal organisms have been found to cause disease if the local niche population is disrupted by either physical or chemical means such as surgery or drugs (hormones, antibiotics, etc.), respectively
- **1.3.2.** Change of this balance with developing age. It is known that in many humans the bacterial flora changes as we grow older.

1.4. Risk factors of changing microecology

- **1.4.1.** Aging
- **1.4.2.** Diet
- **1.4.3.** Antibiotic overuse
- **1.4.4.** Long-term corticosteroid intake
- **1.4.5.** Alcohol abuse
- **1.4.6.** Immune suppression
- **1.4.7.** Surgery

A.2. MAIN ISSUES TO BE RESOLVED

2.1. Investigations into changes in "microflora-organism" ecosystem in the course of aging

2.2. Establishing the individual microbiota-profiles, and changes during aging

2.3. Investigations into the influence of risk factors on the state of "human organism-normal flora" system

2.4. Research study of age-related changes in interaction of microflora and organism immune system

2.5. Research study of molecular interactions between organism and its microflora in the course of aging

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Microflora dynamics as a function of age – specific population and/or species changes/disturbances

- **3.1.1.** Age related changes in epithelium interacting with microflora, its frontal systems:
  - **3.1.1.1.** Glycoprotein Antigens
  - **3.1.1.2.** Lactoferrin
  - **3.1.1.3.** Local immunity systems (s-IgA)
- **3.1.2.** Age related changes in the pre-epithelium which is a matrix that includes:
  - **3.1.2.1.** Bacterial glycocalyx
  - **3.1.2.2.** Exposed glycoproteins of epithelial cells
  - **3.1.2.3.** Epithelial polysaccharides
  - **3.1.2.4.** Polysaccharides with distribution of low-molecular metabolites of different origin
  - **3.1.2.5.** Mineral ions
  - **3.1.2.6.** Organic ions
- **3.1.3.** Age related changes in the state of barrier body tissue
- **3.1.4.** Age-related changes in metabolic activity of microflora in specific niches such as:
  - **3.1.4.1.** Gastrointestinal
  - **3.1.4.2.** Urogenital
  - **3.1.4.3.** Oropharyngeal
- **3.1.5.** Age-related changes in output of bioactive compounds from microflora and will include studies of up and down regulation of compounds such as:
  - **3.1.5.1.** Vitamins
  - **3.1.5.2.** Hormones
  - **3.1.5.3.** Antibiotics

3.1.5.4. Toxins
3.1.5.5. Lipids
3.1.5.6. Alcohols
3.1.5.7. Unknown bioactive compounds

3.2. Risk Factors for the changes of the "normal" microflora in the human system

3.2.1. Disease, primarily gastrointestinal disease

3.2.2. Infections – bacterial, parasitic or viral

3.2.3. Stress, especially chronic stress

3.2.4. Irregular or unbalanced diet, chronic and willful diet imbalances

3.2.5. Iatrogenic effects such as:
3.2.5.1. Antibacterial therapy
3.2.5.2. Hormonotherapy
3.2.5.3. Cytostatics usage
3.2.5.4. Radiation therapy
3.2.5.5. Surgery

3.2.6. Xenobiotics of different origin

3.2.7. Biorhythm disorders

3.2.8. Excessive background radiation

3.2.9. Magnetic disturbances

3.3. Modulation of the immune system by the microflora and dynamics of the microflora induced by the body's innate immune system – a vice-versa relationship

3.3.1. Age-related or age dependent modulation of the immune system via the phenomenon of "mutual molecular mimicry" (whereby microflora mimics receptors/antigens of macroorganism and vice-versa)

3.3.2. Modulatory action gastrointestinal microflora on output of cytokines (host defense molecules) with a wide range of biological action

3.3.3. Age-related bacterial population changes that lead to the organism's immune system to consider its own bacteria as foreign (or immunologically extraneous) and its negative consequences on the host organism.

3.4. Molecular interactions between organism and its microflora as a function of age

3.4.1. Metabolism-participating low-molecular particle elements of various classes

3.4.2. Participation of bacterial modulins (modulatory compounds) in regulation of hemodynamic parameters of physiological activities such as microcirculation in various organs, blood coagulability and flow properties, hormones synthesis, pulmonary ventilation etc. These modulins can include but are not limited to compounds such as:

3.4.2.1. Histamine
3.4.2.2. Thrombotonin
3.4.2.3. Prostaglandins
3.4.2.4. Leukotrienes
3.4.2.5. Free radicals
3.4.2.6. Platelet-activating factor, etc.

3.4.3. Microbial metabolites and metabolite mediators on modulation of proliferation, cell-differentiation, apoptosis and metabolic reactions of eukaryotic cells at a cellular and tissue level.

3.4.4. Molecules that mediate bacterial adhesion, cellular adhesion and microflora population growths. These can include but are not limited to:
3.4.4.1. Oligomeric molecules or protein oligomers
3.4.4.2. Desquamated epithelium cells
3.4.4.3. Organellas
3.4.4.4. Large toxins
3.4.4.5. Quorum-sensing molecules
3.4.4.6. Hypercomplex formations of pre-epithelium layers

3.4.5. Physico-chemical processes and parameters conditioning homeostasis of contact areas such as:
3.4.5.1. Local acid-base conditions
3.4.5.2. Capacitance
3.4.5.3. Oxidation-reduction
3.4.5.4. Rheological conditions
3.4.5.5. Buffered characteristics, etc.

3.4.6. Molecular-dynamic process, folding and refolding, conformation transitions, i.e. changing of molecular geometry on no account of chemical reactions, but repacking through cooperative recombination of various intermolecular contacts

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. PERSONALIZED MEDICINE

1.1. Personal microflora and microbiotoa profile determination

1.2. Age-dependent microflora characterization

1.3. Maintenance of microflora population at expected age levels

B.2. PROBIOTICS

- **2.1.** Friendly live bacterial cultures as food supplements
  - **2.1.1.** Active yoghurt cultures
  - **2.1.2.** Nutritional tablets
  - **2.1.3.** Personalized/generalized microflora tablets

B.3. MOLECULAR INTERVENTION STRATEGIES TO TREAT DISEASE INVOLVING NICHE MICROFLORA DISRUPTIONS

- **3.1.** Specific protein analysis using antibody markers
- **3.2.** Biomarker discovery
- **3.3.** Metabolites as markers for disease onset prediction
- **3.4.** Discovery of metabolite inhibitors or binders to turn on/off processes
- **3.5.** Microbiome (Microflora genome) characterization as a means of understanding other complex diseases such as cancer and auto immune disorders
- **3.6.** Modulation of microflora for control of allergy or allergic symptoms

Section **13**

REPRODUCTION AND AGING

BIOLOGICALLY, AGING IS GENERALLY considered as a post-reproductive emergent phenomenon. In evolutionary life histories of animals, fast maturation, early reproduction and high reproductive output are associated with short lifespan; whereas slow maturation, late reproduction and low reproductive output are associated with long lifespan. Although genetic factors that link reproduction and aging are being discovered, detailed molecular studies that characterize these factors in different organisms and humans are required. Such studies would shed more light on the molecular mechanisms that link aging and reproduction and possibly could make it possible to decouple reproduction from aging in humans in order to prolong either the reproductive potential or the lifespan or both.

(A) BASIC RESEARCH ASPECTS

A.1. ALREADY ESTABLISHED FACTS

1.1. Age-dependent alteration of reproduction in terms of:

1.1.1. Imbalance of sex hormones

1.1.2. Decrease in libido

1.1.3. Mutations and chromosome aberrations in germ cells

1.1.4. Apoptosis of germ cells

1.2. Reproduction-dependent alteration of senescence

1.2.1. Removal of germline in Drosophila and C. elegans increases longevity by 60%

1.2.2. Pregnancy shortens lifespan

1.2.3. Delayed reproduction leads to delayed aging

1.2.4. Highly social mole-rats and social insects are exceptions to the rule

1.2.5. Complex interaction between reproductive signals and other signalling pathways

1.2.6. Hormonal pathways controlling reproduction and longevity act independently and can be decoupled

A.2. MAIN ISSUES TO BE RESOLVED

2.1. How valid is the 'Grandmother effect'?

2.2. Can reproduction be decoupled from aging in humans?

2.3. What is the effect of reproduction on longevity of males as compared to females?

2.4. What are the harmful and beneficial consequences of post-reproductive changes in hormones?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

1.1. Metabolic causes of decrease in reproduction

1.1.1. Association between glucose and fatty acids metabolism and cholesterol metabolism

1.1.1.1. Hepatic steatosis and atherosclerosis

1.1.1.2. Gallbladder cholesterosis

1.1.1.3. Insulin resistance and atherosclerosis

1.1.1.4. Gender-specific metabolism of cholesterol

1.1.1.5. Lipid metabolism and synthesis of sex hormones

1.1.2. Role of sex hormones in energy substrate metabolism

1.1.2.1. Estrogen and adipose tissue

1.1.2.2. Androgens and muscle tissue

1.2. Mechanisms of antagonism between reproduction and longevity

1.2.1. Endocrine influence on somatic tissues

1.2.2. Redistribution of plastic and energy resources from soma to germ

1.2.3. Behavior expenditures for reproduction

1.3. Mechanism of antagonism between reproduction and longevity in social insects and negligible effect of reproduction on longevity in mole-rats

1.3.1. Difference in endocrine influence as compared to other organisms

1.4. Cross-gender effects on longevity

1.4.1. Influence of males on longevity of females and vice-versa

1.4.2. Maternal effect

1.5. Mechanism of sex differences affecting life-span

1.5.1. Social component

1.5.1.1. Genetic reasons for behavioural risks in males

1.5.2. Biological component

1.5.2.1. Heterogametic and homogametic sexes

1.5.2.2. Differences in neuroendocrinal regulation between sexes

1.5.2.3. Telomere truncation speed relative to the sex

1.5.2.4. Differences of antioxidant capacity between sexes

1.5.2.5. The "Grandmother effect"

1.5.2.6. Metabolic features during pre- and post-menopause in females

1.5.2.7. Senescence in males

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. PERSONALIZED MEDICINE

1.1. Determination of genetic markers (e.g., lipid metabolism, hormonal homeostasis) for accelerated aging in the context of reproduction

1.2. Counselling to reduce/counter the impact of presence of genetic markers

B.2. MOLECULAR INTERVENTIONS TO ENABLE CHILDBEARING

2.1. in older individuals without accumulation of mutations

2.2. in younger individuals with problems in conception

B.3. MOLECULAR INTERVENTIONS TO DECOUPLE REPRODUCTION AND AGING

Section **14**

ENVIRONMENTAL INFLUENCE ON AGING

ENVIRONMENTAL FACTORS, both natural and man-made, play crucial role in determining the lifespan of organisms. It has been shown that while genes account for only 25% to 35% variation in lifespan, it is the enrivonmental factors which account for 65% to 75% of the variation in longevity. Life-style related factors, including socio-economic factors affect human life expectancy. The association between environmental factors and increased health-risk, and increased chances of death in older people is well known. However, it is important to establish the difference between how aging increases susceptibility to the environment and how environment alters the rate of aging. Aging and age-related morbidity are multifactorial in nature, and include non-controllable elements like genetic disposition, and more easily controllable elements like environment and life-style. It therefore is important to recognize and study these environment and life-style related factors, so that these could be removed from the equation of aging to prolong lifespan.

(A) BASIC RESEARCH ASPECTS

A.1. ALREADY ESTABLISHED FACTS

1.1. Aging leads to a reduction in homeostasis/homeodynamics

1.1.1. Innate immunity alterations during aging

1.1.2. Acquired immunity changes during aging

1.1.3. Circadean rhythm homeostasis

1.1.4. Water and ion homeostasis

1.2. Environmental factors affect aging and age-related diseases

1.2.1. Involvement of the reactive oxygen species (ROS) and other free radicals generated through various routes

1.2.1.1. Radiation

1.2.1.2. Redox-active metal ions

1.2.1.3. Pollutants

1.2.1.4. Toxins

1.2.1.5. Xenobiotics

1.2.1.6. Nutrients

1.2.1.7. Pharmaceuticals

1.2.1.8. Detergents

1.2.1.9. Allergens

1.2.1.10. Medical and cosmetic procedures

1.2.2. Redox-inert metals, like Aluminium, have a role in age-related diseases

1.2.3. Dietary modulation

1.2.3.1. Food resources («mono-nutrition»)

1.2.3.1.1. Fish and seafood (poly-unsaturated fatty acids)

1.2.3.1.2. Red wine (polyphenols)

1.2.3.1.3. Olive oil (oleic acid)

1.2.3.1.4. Cruciferers (antioxidants)

1.2.3.1.5. Apples (pectin)

1.2.3.2. Caloric restriction

1.2.3.2.1. Animal-based versus plant-based diet

1.2.3.2.2. Totally fat-free diet

1.2.3.2.3. Saturated fat-free diet

1.2.3.2.4. Slowly digested carbohydrates

1.2.4. Negative effects of modern food growing and processing techniques in aging and age-related diseases

1.2.4.1. Chemical fertilizers, pesticides, preservatives

1.2.4.2. Trans-fats

1.2.5. Positive effects of diet supplementation with vitamins and minerals

1.2.6. Effect of temperature on aging

1.2.6.1. Effect of lowered ambient temperature on lifespan extension

1.2.6.2. Temperature-induced hormesis

1.2.6.3. Heat shock proteins and other chaperones

1.3. Socio-economic factors affect aging and longevity

1.3.1. Poverty

1.3.2. Living conditions

1.3.3. Working conditions

1.3.4. Social stresses

A.2. MAIN ISSUES TO BE RESOLVED

2.1. Which modifications of the environment can improve health and survial?

2.2. What is the link between exposure to certain environmental/lifestyle factors at younger ages and health and survival in later life?

2.3. What are the individual responses to variations in environamental conditions?

2.5. What is the realtionship between external and internal factors which induce stress?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Oxidative stress and aging

3.1.1. Verification of the 'rate of living' theory

3.1.2. The influence of oxygen pressure on longevity

3.1.3. Pathways and mechanisms of protein repair

3.2. Pathways of chronic inflammation in aging cells

3.3. Diet and aging

3.3.1. Diet analysis as potential aging rate regulator

3.3.2. Molecular mechanisms of diet supplementation

3.3.3. Molecular mechanisms of effects of caloric restriction and mononutrition

3.4. The mechanisms of temperature influence on rate of aging

3.5. Light regimes and aging

3.5.1. Intensification of vital activity at light as aging-accelerating factor

3.5.1.1. Mechanisms of reproduction activation

3.5.1.2. Change of ratio between rest and activity

3.5.2. Suppression of neuroendocrinal regulation in dark regime

3.6. Ionizing radiation and aging

3.6.1. Pathways of radiation hormesis

3.6.2. Mechanisms of radiation adaptive response

3.6.3. Hyper-radiosensitivity and acceleration of aging

3.6.4. Radiation-induced oncogenesis

3.7. Mechanism of action of redox-inert metals in causing age-related disease

3.8. Variable gravity and longevity

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. DEVELOPING INDIVIDUAL-SPECIFIC FUNCTIONAL GENOMICS AND PROTEOMIC PROFILES FOR MONITORING IMMEDIATE AND DELAYED RESPONSES TO ENVIRONMENTAL FACTORS

B.2. STRATEGIES FOR THE DEVELOPMENT OF PERSONALISED MEDICINE

2.1. Development of lab-on-a-chip technology to monitor toxic bioaccumulation

2.2. Development of bio-assays that are provided to primary healthcare providers so that along with standard blood testing and other laboratory tests that one undergoes

2.3. Development of metal-chelator drugs that could be used to maintain the "healthy level" of any particular metal in the human body

B.3. STRATEGIES AND PRODUCTS TO IMPROVE CLEARANCE MECHANISMS OF DAMAGED PROTEINS

3.1. Drugs for improving protein folding

3.2. Drugs for increasing chaperone activity

3.3. Drugs for improving protein degradation activity

B.4. CREATION OF GERONTOTOXICOLOGICAL DATABASES - INCLUDING NEUROTOXICOLOGICAL AND IMMUNTOXICOLOGICAL EFFECTS OF ENVIRONMENTAL FACTORS. LINK WITH DATA RELATED TO HORRMETIC LEVELS.

B.6. EPIDEMIOLOGICAL DATA COLLECTION ON EARLY EXPOSURE LEADING TO AGE-RELATED DISORDERS LATER IN LIFE.

Section **15**

SEARCH AND DEVELOPMENT OF GEROPROTECTORS

GEROPROTECTORS ARE ANY SUBSTANCES, conditions and their combinations which can help to maintain youthful state of health, to slow down age-related functional impariments, to prevent or delay the onset of age-related diseases, and to enhance healthspan. All aging research, knowingly or unknowingly, incorportes strategies for discovering novel and effective geroprotectors.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Experimental modulation of aging, healthspan and lifespan is possible, at least in model systems

1.1.1. Caloric restriction as a geroprotector

1.2. Other known potential geroprotectors

1.1.2. Anti-diabetic drugs

1.1.2.1. Metformin

1.1.2.2. Diabenol

1.1.2.3. Buformin

1.1.3. Hormones

1.1.3.1. Thyroxine

1.1.3.2. Prednisolone

1.1.3.3. DHEA

1.1.3.4. Melatonin

1.1.4. Biological cycle intermediates

1.1.4.1. Saline succinate

1.1.5. Neurotropic drugs

1.1.5.1. Phenytoin

1.1.5.2. Depranyl

1.1.6. Peptides or peptide based mimetics

1.1.6.1. Epitalamin and epitalon

1.1.6.2. Vilon

1.1.7. Antioxidants

1.1.7.1. Vitamin E

1.1.7.2. Coenzyme Q-10

1.1.7.3. Beta carotene

1.1.8. Herbs, plants, adaptogens, hormetins

1.1.8.1. Gingko biloba

1.1.8.2. Ginseng

1.1.8.3. Polyphenolic compounds

1.1.8.4. Flavanoids

1.1.8.5. Spices

A.2. MAIN ISSUES TO BE RESOLVED

2.1. What is the molecular basis of the action of geroprotectors in model systems?

2.2. Do geroprotectors work across species, specially in humans?

2.3. How to screen for potential geroprotectors in humans?

2.4. Can we combine multivariate analysis to assess the multiple downstream effects of geroprotector usage?

2.5. How to link extrinsic (environment) and intrinsic (microbiota) factors together with geroprotectors?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

1.1. Identifying and developing the molecular basis of geroprotectors

1.1.1. Improved screening

1.1.2. High throughput screening methodology development

1.1.3. Methodology development to simultaneously screen for protective vs. toxic effects

1.1.4. Changes in cell signalling pathways

1.1.5. DNA repair activation

1.1.6. Cytokine modulation

1.1.7. Natural antioxidant mechanism induction

1.1.8. Sirtuin chain modulation

1.1.9. Biomarker discovery

1.1.10. Chaperone activity modulation

1.2. Improvement of classification of geroprotectors:

1.2.1. Applying molecular data for classification basis

1.2.2. Wide scale correlation of epidemiology of "aging markers" to rate of basic age-related diseases (diabetes, atherosclerosis, Alzheimer's disease etc.), accidents (myocardial infarction, cerebral accidents), incapacitation and death

1.2.3. Collation of pathophysiological data

1.2.4. Establish correct pathomorphologic criteria of death cause definition in laboratory animals (e.g. primates)

1.2.5. Create a scheme-listing of required integral indications and model systems for geroprotectors' screening

1.3. Expand molecular basis of known geroprotectors and extension to human trials

1.3.1. Melatonin

1.3.1.1. Effect on cell transformation, apoptosis and senescence

1.3.1.2. Regulatory effect in CNS

1.3.1.3. Effect on telomerase expression and telomere length

1.3.1.4. Impact on free-radical generation in mitochondria

1.3.1.5. Impact on hormone secretion

1.3.2. Peptide and peptide mimetics

1.3.2.1. Continuation of analysis of fractions peptide extracts of thymus and epiphysis extracted by different methods; research of their geroprotective activity

1.3.2.2. Effect on gene expression patterns
1.3.2.3. Performance of APUD systems
1.3.2.4. Adregenic and nor-adregenic modulation
1.3.2.5. Peptide clearance and adsorption

1.3.3. Growth hormone
1.3.3.1. Effect on IGF-1 receptors
1.3.3.2. Effect of GH expression as a function of caloric restriction
1.3.3.3. Screening for IGF-1 receptor agonists

1.3.4. Adaptogens and hormetins
1.3.5. Drugs
1.3.6. Neurotropic drugs
1.3.7. Antioxidants
1.3.8. Calorie restrcition mimetics

1.4. Development of guidelines for geroprotective research
1.4.1. Experiment model selection
1.4.2. Selection of physiological age markers
1.4.3. Development of unified test reports on potential geroprotectors efficiency in animals (monkeys, rats, mice, fruit flies, hookworms, yeast).
1.4.4. Development of preclinical and clinical testing guidelines

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. DEVELOPMENT OF GEROPROTECTOR SCREENING KITS FOR LABORATORIES

1.1. High throughput screening development
1.2. Biomarker identification of geroprotector use

B.2. DEVELOPMENT OF MULTIPLE APPLICATIONS OF GEROPROTECTORS

2.1. Increased application screening
2.2. Coupling of population profiling with geroprotector use
2.3. Environmental effects on geroprotectors
2.4. Regulatory market development for guideline development and application use of geroprotectors.

B.3. DEVELOPMENT OF SPECIFIC GEROPROTECTORS IN THE FORM OF:

3.1. Nutritional supplements
3.2. Topically applied products
3.3. Medical therapeutic substances, including drugs, injections, surgery-mediated applications

Section **16**

IDENTIFICATION OF MOLECULAR MARKERS IN AGING

HUMAN AGING IS NORMALLY measured chronoligcally and many age-related disorders, which are a direct consequence of aging, are described based on an individual's chronological age. However, chronological age may not always reflect the true consequences of an aging body whereby multiple changes are taking place simultaneously and, many-a-time, much earlier than visible signs of aging. It is therefore one of the priority areas that molecular markers of aging be identified which would be much more accurate in pedicting the "real biological-age" of the human body and the consequent prediction of onset of age-related disorders.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Good and comparative model systems of longevity and aging

1.1.1. Naked mole rat (life expectancy of 25-28 years)

1.1.2. Close relative of naked mole rat – shrew mouse (life expectancy 2-3 years)

1.1.3. Podospora and other fungal species

1.1.4. Long-lived and short-lived worm models (C. elegans)

1.1.5. Long-lived females of social insects (bees, wasps, ants etc.)

1.2. Establishment of multiple organ, tissue and system models of aging:

1.2.1. Brain aging

1.2.2. Skin aging

1.2.3. Muscle aging

1.2.4. Bone aging

1.2.5. Immune system

1.2.6. Endocrine system

1.2.7. Reproductive system

1.3. Molecular changes in aging

1.3.1. Altered gene expression

1.3.2. Altered protein amounts and activities

1.3.3. Macromolecular damage accumulation

1.4. Importance of epigenetic modulation in aging and longevity – and their influence in the search of biomarkers

1.4.1. Methylation

1.4.2. Acetylation

1.4.3. Other modifications

A.2. MAIN ISSUES TO BE RESOLVED

2.1. Can comparative biology approaches using relevant animal models lead to the discovery of novel biomarkers of aging?

2.2. Will there be one or multiple biomarkers of aging?

2.3. Can we monitor the performance of regulatory systems in the human body to identify and characterise the biological aging process?

2.4. Are non-invasive methods for measuring molecular age a real possibility?

2.5. What is the best biological sample (saliva, urine, blood, tissue biopsy) for biomarker studies?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

1.1. Relationship between the model system and human aging biomarkers

1.1.1. Investigating multiple parameters within the same model system

1.1.2. Use of a mix of invasive and non-invasive methods

1.1.3. Intelligent parameter choice with parameters defined as being those with intervals of 10-20% from the average life expectancy.

1.1.4. Investigate lifespan diversity in different lines of the same species

1.1.5. Greater number of experimental organisms to improve statistical variability and enhanced reliability

1.2. Currently known or under discovery biomarkers

1.2.1. p16INK4a

1.2.2. Telomere and telomerase

1.2.3. Oxidative damage

1.2.3.1. DNA (8-oxoguanine)

1.2.3.2. Protein (carbonylation)

1.2.3.3. Lipids (malondialdehyde and 4-hydroxynonenal)

1.2.4. Mt DNA deletion

1.2.5. Heat shock proteins

1.2.6. Apolipoprotein levels

1.2.7. Antioxidative enzymes

1.2.7.1. Thioredoxin

1.2.7.2. Peroxiredoxin

1.2.7.3. Superoxide dismutase

1.3. Human research and application of non-invasive methodology

1.3.1. Attraction of human volunteers (aged 20 – 80) in statistically significant numbers (> 1000)

1.3.1.1. Mono- and di-zygotic twins

1.3.1.2. Families with long-lived relatives

1.3.1.3. Centenarians

1.3.2. Collection of preliminary health info and history from each volunteer

1.3.3. Blood as an important resource to look for potential biomarkers; efficacy of already seen biomarkers such as:

1.3.3.1. Cytokines

1.3.3.2. p16INK4a

1.3.4. Data collection from various methodologies and tests:

1.3.4.1. Behavioral

1.3.4.2. Psychological

1.3.4.3. Biochemical

1.3.4.4. Genetic

1.3.4.5. Social
1.3.4.6. Demographic
1.3.4.7. NMR
1.3.4.8. PET

1.3.5. Full genetic sequence analysis
1.3.5.1. SNP identification and library

1.3.6. Mathematical and statistical model building of large scale data and data integration

1.4. State-of-the art methodology development
1.4.1. Large scale proteomics
1.4.2. Large scale genomics
1.4.3. RNA (mRNA expression profiles)
1.4.4. Search for newer biomarkers

1.5. Investigation of tissue and cell antioxidant defense state

1.6. Evaluation of integral antioxidant potential

1.7. Characterization of biological structures resistance to induced oxidation

1.8. Development of tissue oxidative and carbonyl stress quantitative evaluation methods (express methods for measuring protein carbonyls, malone dialdehyde, methylglyoxal, homocystein and other metabolites)

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. DEVELOPMENT OF KITS FOR PERSONALIZED GENOMICS

1.1. Development of early-stage age-related disorder detection/diagnosis kits

1.2. Counselling market to explain consequences of age and age/related disorders
1.2.1. Genetic counselling
1.2.2. Biochemical counselling
1.2.3. Psychological counselling

B.2. DEVELOPMENT OF "LAB-ON-A-CHIP" KITS TO ALLOW DETECTION OF NUMEROUS MOLECULAR AND BIOCHEMICAL MARKERS

B.3. DEVELOPING TECHNIQUES ALLOWING ONE TO ESTIMATE THE CELLULAR STRUCTURE AND FUNCTIONAL CONDITION OF THE CELLS IN THE TISSUE BY NONINVASIVE WAY, IN VIVO;

B.4. DEVELOPING A MATHEMATICAL APPARATUS FOR THE ANALYSIS OF THE RESULTS ON SEARCH OF THE AGING BIOMARKERS.

Section **17**

MATHEMATICAL MODELLING OF LONGEVITY AND AGING

BIOLOGICAL SYSTEMS AND BIOLOGICAL PROCESSES, such as aging and longevity, are highly complex, interacting and dynamic. The normal reductionistic anlaytical approaches have a limited penetration in elucidating various layers and orders of complexity. This issue becomes even more challenging when population and evolutionary dynamics need to be incorporated in any analysis and in attempts for making reliable future projections, predications and strategy solutions. The emergence and application of statistical and mathematical modeling tools is facilitating such studies in aging research and intervention.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. Increase in quantification of aging data and development of mathematical models

1.1.1. Multiple modeling systems

1.1.2. Dynamical system analysis

1.1.3. Methodological developments to handle complex data

1.1.3.1. Better computational power

1.1.3.2. Increased understanding of complex data

1.1.3.3. Better mathematical models

1.1.4. Template development of mathematical modeling:

1.1.4.1. Metabolic systems

1.1.4.2. Endocrine systems

1.1.4.3. Enzymatic reactions

1.1.5. Co-evolution of empirical models and theoretical models

1.1.5.1. Empircal models

1.1.5.2. Theoretical models

1.1.5.3. Systems biology approaches

1.2. Establishment of Gompertz law and its modifications, such as Gompertz–Makeham equation

1.2.1. Development of models analyzing population heterogeneity in aging

1.2.2. theory

1.3. In-silico modeling of various neurodegenerative diseases

A.2. MAIN ISSUES TO BE RESOLVED

2.1. What will mathematical models of aging tell us?

2.2. Can the predictions and theoretical sciences help us in understanding the multiple factors involved in aging?

2.3. Can we model theoretical changes of increasing lifespan in a model organism and predict its molecular changes or better still model its changing network biology?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Mathematical analysis of biological control processes in aging

3.1.1. Investigation of the influence of biological processes in aging and elaboration of the subsequent mathematical models

3.1.2. Development of quantitative developmental biology

3.1.3. Investigation of protective systems in an organism and modeling its effects on life span

3.1.4. Quantification of regulatory systems and feedback control in humans

3.2. Modeling normal and pathologic aging

3.2.1. Quantifying influence of allostatic load on aging and survival processes

3.2.2. Investigating effects of oxidation and load of increased oxidative stress as a function of age

3.2.3. Modeling of healthy organisms

3.2.4. Modeling of age-specific morbidity

3.2.5. Modeling of various age-related disease states

3.3. Aging and optimality of biological systems

3.3.1. Mathematical modeling of the evolutionary optimal strategies for development, reproduction and survival

3.3.2. Mathematical modeling of the individual patterns of the evolutionary optimal strategy realization using individual data on reproduction and longevity (egg laying by drosophila)

3.3.3. Modeling of macrobiotic species nascency as a consequence of individual peculiarities of recourses distribution

3.3.4. Modeling of individual and population mechanisms of reproductive and post-reproductive distribution of resources from the point of view of optimal longevity

3.4. Modeling intrinsic and extrinsic effects in aging

3.4.1. Intrinsic effects

3.4.1.1. Perturbed homeodynamics

3.4.1.2. Biochemical infidelity

3.4.1.3. Nutritional metabolites

3.4.2. Extrinsic effects

3.4.2.1.

3.4.2.2.

3.4.2.3. Evolutionary slection pressure

3.4.2.4. Environmental alterations

3.5. Mathematical models of aging of physiological systems

3.5.1. Nervous system

3.5.2. Regulatory system

3.5.3. Bioenergetics

3.5.4. Age-dependent senescence on energetic

3.5.5. Cell division and morphogenesis

3.5.6. Sub-cellular transport

3.5.7. Ontogenesis control system

3.5.8. Hematopoetic

3.5.9. Reproductive system

3.5.10. Hormonal system

3.6. Development of virtual models of aging

3.7. Mathematical modeling of longevity and lifespan

3.7.1. Development of models to forecast lifespan in model organisms

3.7.1.1. Definition of genetic determinants

3.7.1.2. Impact of environmental changes in lifespan

3.7.1.3. Impact of improved health care in lifespan

3.7.2. Mathematical models for healthy lifespan (

3.7.2.1. Development of age-specific biological indicies

3.7.2.2. Mathematical modeling of biological age

3.7.2.3. Impact of physical/mental disability on life span

3.7.2.4. Mathematical models of hormesis

3.7.2.5. Caloric restriction

3.7.2.6. Reproductive restriction

3.7.2.7. Genetic modifications

3.7.2.8. Influence of socio-economic, cultural, ethnic and religious factors on lifespan

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. DEVELOPMENT OF METHODOLOGY FOR MODELING PROCESSES OF AGING, LOSS OF HEALTH AND LONGEVITY FOR RESEARCH, DIAGNOSIS AND INTERVENTIONS

1.1. Development of computer aided methodology for aging modeling

1.1.1. Analyses of specialized computer languages and systems for aging modeling (Simula, SBML and other)

1.1.2. Development of computer models based on evolutionary principles in humans and in animals

B.2. DEVELOPMENT OF SOFTWARE, HARDWARE AND USER-FRIENDLY "MATHEMATICAL MODEL BOX PACKS" TO ACADEMIC AND INDUSTRIAL CLIENTS BASED ON ABOVE DATA.

B.3. DEVELOPMENT OF METHODS FOR TRANSITION OF THE RESULTS OF LONGEVITY EXTENSION IN ANIMALS TO HUMANS

Section **18**

PROSPECTS OF BIOINFORMATICS IN THE STUDY OF AGING AND LONGEVITY

BIOINFORMATICS HAS EMERGED to be a powerful tool that assists experimentalists in not only handling large amounts of data and undertaking complex calculations but also making predictions about future trends. Generation of bioinformatic resources uses a large array of machine-learning algorithms and neural networks to predict complex interactions and pattern recognition. Extending the tools of bioinformatics in aging research has a great potential to advance the field and also to predict hitherto unchartered territories of increasing life expectancy. Finally, it is expected that bioinformatics will become part of the larger Systems Biology efforts underway that will bring together bench experimentalists and computational specialists together.

(A) BASIC RESEARCH ASPECTS

A.1. ESTABLISHED FACTS

1.1. The presence of a large number of repositories of varying character and content

- **1.1.1.** DNA databases
- **1.1.2.** RNA databases
- **1.1.3.** Protein databases
- **1.1.4.** Protein Interaction Network (PIN) Databases
- **1.1.5.** Gene regulatory network databases (DNA microarrays)
- **1.1.6.** Evolutionary comparative databases

1.2. Presence of various animal models of aging (in addition to the human cell culture models) from which a lot of comparative data are extracted and compared in the field of comparative bioinformatics. The well known animal models of aging include:

- **1.2.1.** Mouse/Rat model
- **1.2.2.** C. elegans model (roundworm)
- **1.2.3.** Podospora sp. model (fungus)
- **1.2.4.** Saccharomyces cerivisiae (yeast or single celled fungus)
- **1.2.5.** Drosophila melanogaster (fruitfly)
- **1.2.6.** Non human primates like chimpanzees, monkeys
- **1.2.7.** Birds such as the barn swallow (Hirunda rustica) and the collared (flycatcher)

1.3. Text-mining tools and other bioinformatic tools and databases that can be harnessed to study ageing. Examples include:

- **1.3.1.** iHOP
- **1.3.2.** NetAGE
- **1.3.3.** KEGG
- **1.3.4.** EXCERBT
- **1.3.5.** SENNA
- **1.3.6.** BLAST

1.4. Presence of databases specifically of use for biogerontologists

- **1.4.1.** Baltimore Longitudinal Study of Ageing
- **1.4.2.** BodyMap
- **1.4.3.** GeneCards
- **1.4.4.** HPRD
- **1.4.5.** PDB
- **1.4.6.** SAGE KE
- **1.4.7.** Swiss-Prot
- **1.4.8.** EMBL
- **1.4.9.** Telomere database

1.5. Specific analyses that have given some information on the aging landscape but may still need to be expanded include:

- **1.5.1.** Transcriptional regulation of aging
- **1.5.2.** Phylogenetic footprinting
- **1.5.3.** Comparative genomics
- **1.5.4.** Comparative proteomics
- **1.5.5.** DNA microarrays
- **1.5.6.** MicroRNA analysis
- **1.5.7.** SiRNA - gene silencing

A.2. MAIN ISSUES TO BE RESOLVED

2.1. Can comparative genomics ease the study of human ageing?

2.2. Are there any novel mechanisms of genome functioning?

2.3. How to achieve the integrated analysis of molecular regulatory systems?

2.4. How to link extrinsic and intrinsic factors of aging and map the interaction of humans with intrinsic and extrinsic microbiota?

A.3. BASIC RESEARCH FACTS YET TO BE ESTABLISHED

3.1. Developing new methods and algorithms for analysis

- **3.1.1.** for the comparative analysis of data contaminated with noise
- **3.1.2.** to seek associations between different types of polymorphism and life expectancy
- **3.1.3.** to analyze primary data and, in particular, methods to obtain information about the modifications of proteins from mass-spectra and genomes
- **3.1.4.** for seeking the regulatory signals in SELEX results

3.2. Developing methods for analysing genome information:

- **3.2.1.** for seeking regulatory elements such as enhancers and promoters
- **3.2.2.** for comparative analysis of the regulatory elements
- **3.2.3.** for seeking micro-RNA targets
- **3.2.4.** for searching for possible new mechanisms of RNA-regulation, in particular slicing, and the modification of the chromatin structure
- **3.2.5.** for comparative analysis of protein sequences to identify possible sites of post-translation modification and interactions between proteins
- **3.2.6.** to analyze the networks of interaction between proteins
- **3.2.7.** to search and predicting sites of nucleus binding.
- **3.2.8.** to carry out integrated analysis of the genome's functioning taking into account all the information about the nucleus binding sites, transcription factor binding sites, micro-RNA binding sites, methylation of DNA etc.

3.3. Searching for new mechanisms of genome functioning and experimental testing of the predicted mechanisms

- **3.3.1.** for new systems regulating slicing based on known or new classes of small RNA. At this stage there are indirect indicators that such regulation may be possible.
- **3.3.2.** for possible participation of small RNA in genome methylation and in the remodeling of chromatin.

3.4. Integrated analysis of molecular regulatory systems

- **3.4.1.** Information about different kinds of regulatory interactions must be gathered in regulatory networks and cascades that include all known levels:
  - **3.4.1.1.** epigenetic (DNA methylation, chromatin remodeling),
  - **3.4.1.2.** transcription based (promoters, enhancers, polyadenylation, interaction with the chromatin structure), including the transcription of regulatory RNAs,
  - **3.4.1.3.** Splicing (regulation of alternative splicing),
  - **3.4.1.4.** Translational (regulation at the level of micro-RNAs),
  - **3.4.1.5.** Post-translational (post-translational modification of proteins),
  - **3.4.1.6.** Compartmentalization (transport of proteins and RNA to different cell compartments)
  - **3.4.1.7.** Stability of macro-molecules (proteins and RNA).
- **3.4.2.** Regulatory networks must be restored on the basis of all available information
- **3.4.3.** An adequate language needs to be developed to describe regulatory networks.
- **3.4.4.** The reaction of the networks to external input needs to be predicted. The results of the predictions should then be compared with observations when possible.
- **3.4.5.** Bottlenecks need to be identified in regulatory networks to identify locations that are most sensitive to influence, both positive (targets for correction) and negative.

3.5. Linking extrinsic and intrinsic factors of aging and mapping the interaction of humans with intrinsic and extrinsic microbiota for studying

- **3.5.1.** The diversity of the symbiotic micro-organisms living in the stomach and the intestinal tract.
- **3.5.2.** Metabolic reconstruction of metagenomes.
- **3.5.3.** The diversity of metagenomes within populations and from population to population.
- **3.5.4.** The possible interaction between metagenomes and the human genomes.
- **3.5.5.** The intracellular symbiotes and parasites and their interaction with the genome

3.6. Developing databases and web services – with focus on availability and ease of usage

(B) APPLIED AND COMMERCIALLY-VIABLE ASPECTS

B.1. PERSONALIZED GENOMICS

- **1.1.** Development of next-generation sequencing methods and massive cost-reduction could lead to a market of personalized gene/genome sequencing
- **1.2.** Counselling market to educate and explain genome information and its impacts
- **1.3.** Regulatory market development to develop and control safety of genetic information

B.2. MOLECULAR/GENETIC INTERVENTIONS TO PREDICT DISEASE AND TAKE PRE-EMPTIVE MEASURES

B.3. A LARGE REPERTOIRE OF ANTI-AGING MEDICINE – BASED ON SCIENTIFIC AND COMPARATIVE DATA

- **3.1.** Fast-track the anti-aging pharmaceutical search drive
- **3.2.** Effective and ethnic targeted anti-aging treatments
- **3.3.** Lifespan predictions and health prognosis software

B.4. DEVELOPMENT OF NOVEL DATABASES

- **4.1.** Market for database storage
- **4.2.** Market for database management
- **4.3.** Information clusters that can be licensed for other disciplines and users

B.5. DEVELOPMENT OF NEW ANALYTICAL TOOLS

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