

PROGRAM RELEASE VERSION • FEBRUARY 2009



SCIENCE
AGAINST
AGING

PROJECT BACKGROUND

Dear Colleagues!

The value of a long and healthy life is obvious to every reasonable person. Therefore, aging is a serious and until now unsolved problem. Slowly but inexorably, aging decreases the quality of life, makes people weak and powerless, prevents the realization of people's aspirations. Sooner or later, it leads to death.

Today, the growing desire for a long, high-quality and healthy life becomes increasingly obvious in developed countries. This is confirmed by the strong demand for fitness, anti-aging services, etc. The share of people who openly express this desire for life extension is growing. According to a public opinion poll conducted in Russia in 2008, 78% of Russians do not ever want to age.

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The problem of aging has become relevant in politics. Demographers warn that in the coming decades aging population and decreased birthrates will place a heavy burden on social security and pension systems in all developed countries. The remaining workforce may become unable to support the growing number of retirees.

Leading gerontologists from 10 countries declared in an open letter that aging can be slowed down and healthy life can be prolonged. We share the view that the problem of aging can be solved in the next few decades and that humankind already has everything necessary.

The problem of aging can be solved in the next few decades

1. Our society has financial resources for solving this problem — a major project to defeat aging would cost only about 30 billion dollars.
2. A large body of knowledge about aging has been accumulated that is being used to create a unified system model of human aging.
3. Powerful new technologies in genomics, drug design, mathematical modeling and other fields make it increasingly possible to control and direct processes inside the human body.
4. Many promising ideas and aging hypothesis that can help solve the remaining problems have been developed.

Unfortunately, these opportunities are not being fully used, the efforts of researchers are largely uncoordinated, science and society do not have a clear overarching goal – to defeat aging.

It has become apparent that to significantly extend human life we must:

1. review the present state of research into curing aging
2. establish scientifically-based goals
3. create a unified research program for fundamental gerontology
4. develop new medical technologies.

The task of eliminating aging is extremely complex — both in terms of science, and in organization, planning and implementation. Separate projects in biophysics, biochemistry, pharmacology, genomics, cryobiology, immunology and other fields should be joined within an integrated scientific framework. Gerontology must set the strategy for development of life sciences. We must realize that life extension is the primary purpose of scientific research. Scientific collaboration will create synergy between different research projects and will allow us to defeat aging faster than with uncoordinated and uncontrolled research. The difference in time — possibly tens of years can — save millions of lives.

To join the efforts of individual scientists, research and health institutions, non-government and political organizations at international coordinating center of the program is needed. It's primary tasks are:

Separate projects should be joined within an integrated scientific framework

1. attracting renowned experts in life sciences and research management to the project
2. creating a scientific and organizational program
3. developing a plan to implement this program
4. promoting this program in social, business, and political circles.

In October 2008 a working group was created to develop and promote a comprehensive program to defeat aging. It was set up in Russia by the "Science for Life Extension" foundation. The project is supported by many Russian and international researchers.

Clearly, to create a comprehensive research program to defeat aging (and to carry out the research) many organizations from different countries need to act together for the project to be finished in reasonable time. Such program should be created and implemented with broad international support of scientists, politicians, businessmen, and society.

We note that most of the program should be organizational and managerial in nature. Its successful realization will consolidate scientists from different countries, consolidate and commercialize intermediate research results, paving the way for attracting large-scale government and international funding.

We understand that to defeat aging is a very difficult task, but mankind has already met similar challenges in the past. The space project, the Human Genome project, construction megaprojects are all successful examples of our abilities. This experience gives us confidence that such an ambitious project to eliminate aging is feasible.

Most of the program is organizational and managerial in nature

We think that all steps to create the program needs to be carefully planned: from defining a common methodology for extraction of expert knowledge to distribution of research topics and funding between different laboratories.

We ask scientists and managers to share their knowledge and experience in creating collaborations, organizing research and using expert knowledge, lobbying and managing large projects.

Contact details:



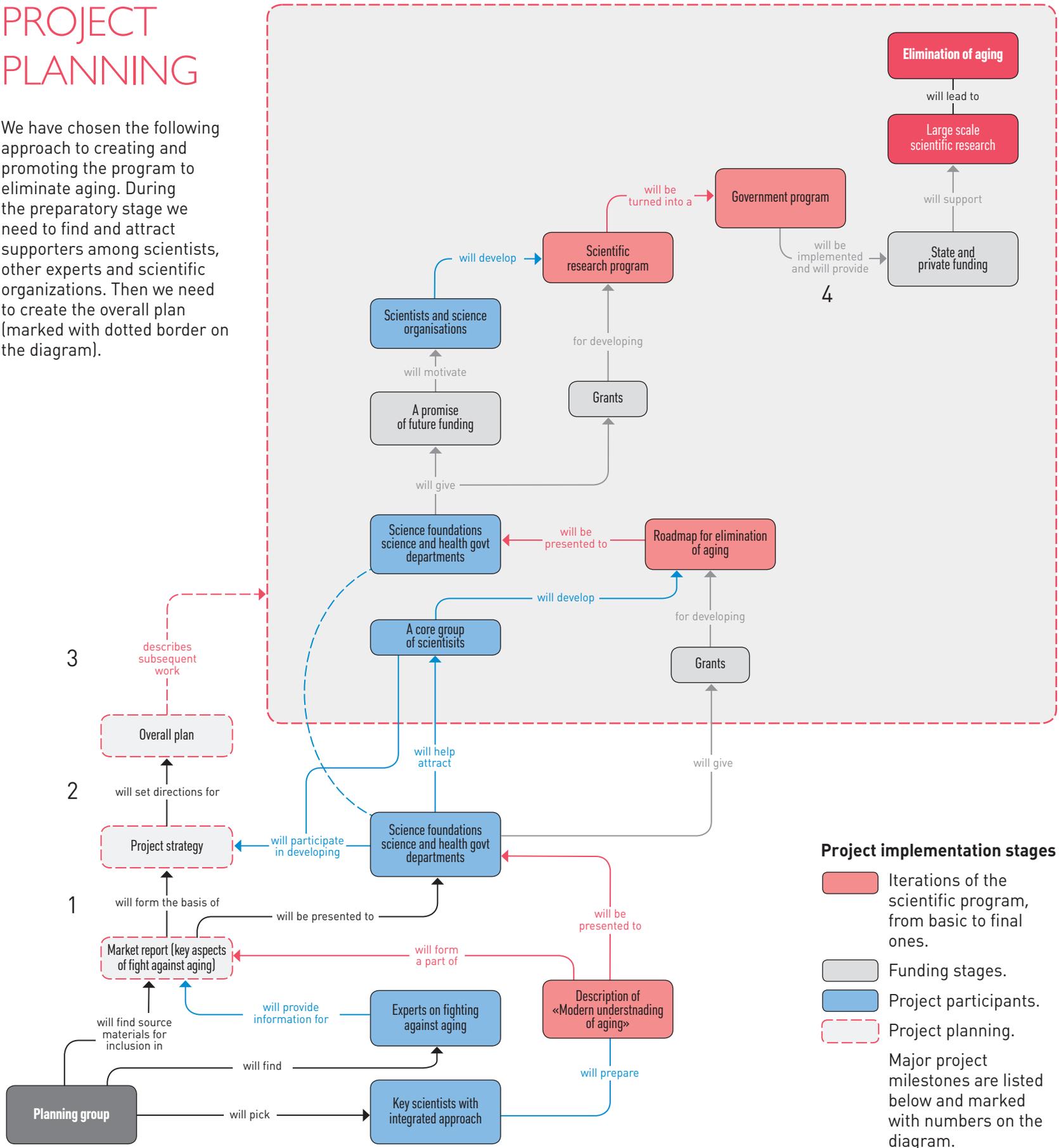
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PROJECT PLANNING

We have chosen the following approach to creating and promoting the program to eliminate aging. During the preparatory stage we need to find and attract supporters among scientists, other experts and scientific organizations. Then we need to create the overall plan (marked with dotted border on the diagram).



The development of the program involves the following stages (deliverables marked in **bold**):

1. Writing an **industry report** (a report on key aspects of fight against aging).
2. Developing the **project strategy**.
3. Creating a detailed **implementation plan**.
4. Developing a **scientific program** to eliminate aging.
5. Lobbying for the finished program.

The program to eliminate aging should be promoted and lobbied for in national governments, to international organizations, among private sponsors and investors.

The first step in our project is to write a review of key aspects of fight against aging (a market report) so that potential partners, experts, sponsors and everyone else could see the overall picture of the struggle to defeat aging.

We invite you to join now the discussion about ways and means to combat aging organized by our foundation, while this review is being prepared and later during the project planning. Describe your vision of the scientific program, help excite the society about research into mechanisms of aging, share your experience in relevant fields. We are always open to co-operation and are glad to get in touch with you!

A REPORT ON KEY ASPECTS OF FIGHT AGAINST AGING

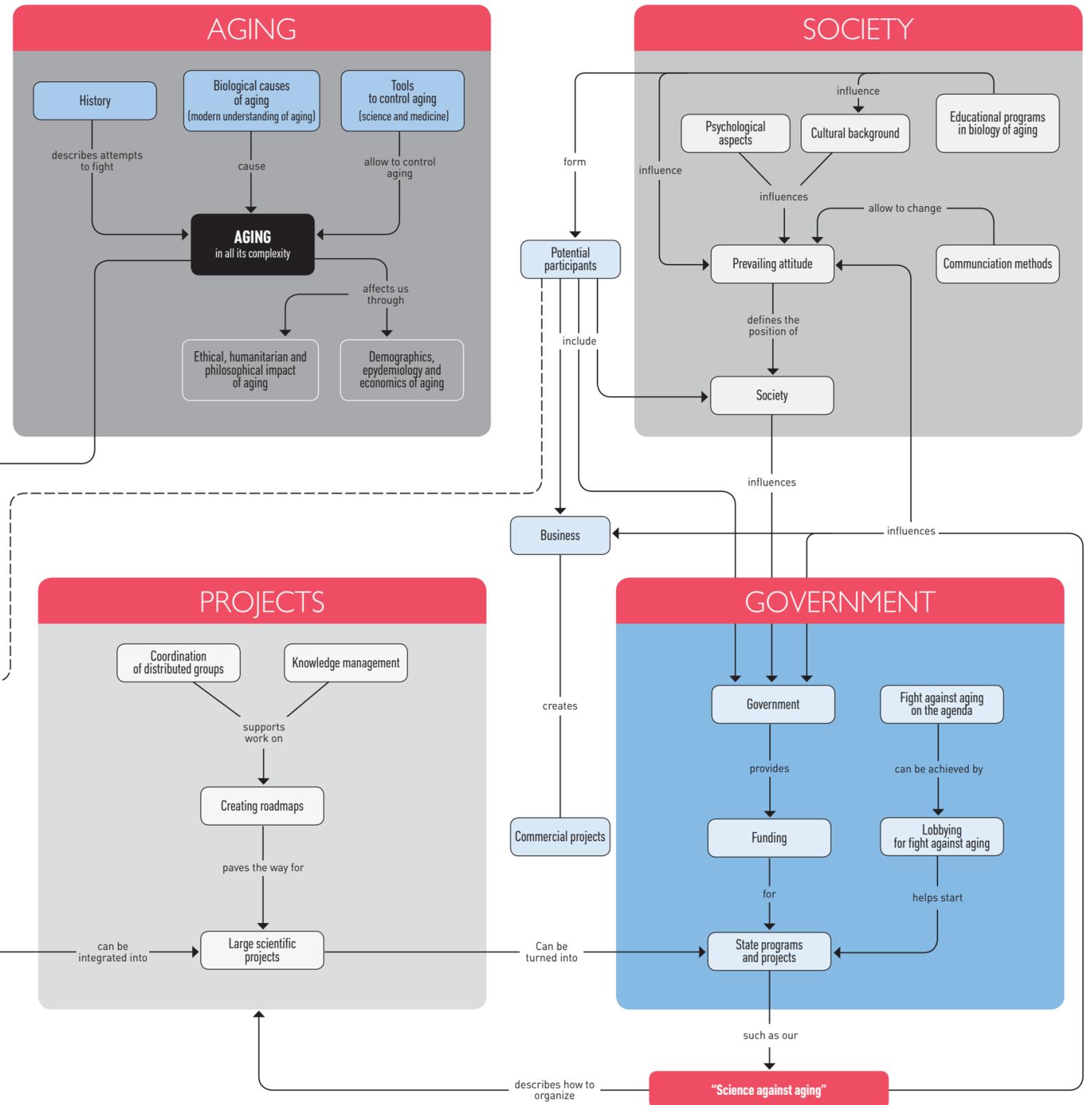
Right now the foundation project team works on the first major deliverable – a report about the fighting against aging field. This document will shed some light on a very uncertain area and will provide participants with basic knowledge about this topic. Once it's completed, participants, experts, journalists, politicians and the public will be able to get a comprehensive understanding of all aspects related to aging that are important for project success.

This document will provide participants with basic knowledge about the field we work in

We call for directors of science organizations, lobbyists, sociologists, public relations specialists, financiers, methodologists and all professionals interested in fighting aging to provide any possible assistance to the project. The first round of consultations with experts is under way. This includes individual interviews with experts and work sessions with several (3-5) specialists. During the sessions additional questions to explore are formulated, while the information gathered is included in the report. As a result knowledge needed for fighting aging becomes available to everyone.

REPORT ON KEY ASPECTS OF FIGHT AGAINST AGING (INDUSTRY REPORT)

The concept map of the report. Large blocks contain major areas described by the report. Smaller blocks represent the main elements of the diagram and their connections show real connections.



UNDERSTANDING AGING AND THE DEVELOPMENT OF SCIENCE PROGRAM

The report section describing modern understanding of aging has significant importance on its own. In this section we will present a coherent description of aging process, its nature and characteristics of human aging. The content will be based on presently available scientific knowledge about aging.

No such description is available yet. Both scientific works on gerontology and popular articles rarely do more than list hypotheses about causes of aging. The information is poorly structured and doesn't form a coherent system.

We plan to work in close contact with leading experts on systems approach to study of aging. We will collect information about key processes that comprise human aging and combine it into a single system illustrated on a single diagram. The level of detail will be determined by practical considerations – we plan to make a general outline before going into details of individual processes. This diagram will show “white spots” that call for further studies and opportunities for interventions in the aging process.

The “modern understanding of aging” diagram will make it possible to communicate our vision of the project

In this section we will highlight key aspects of aging, such as its evolutionary nature, the existence of specific mechanisms of aging, specificity of aging by tissue and organ types and others.

Aging: a system of life, aging and death processes in human organism and possible interventions (overall view).

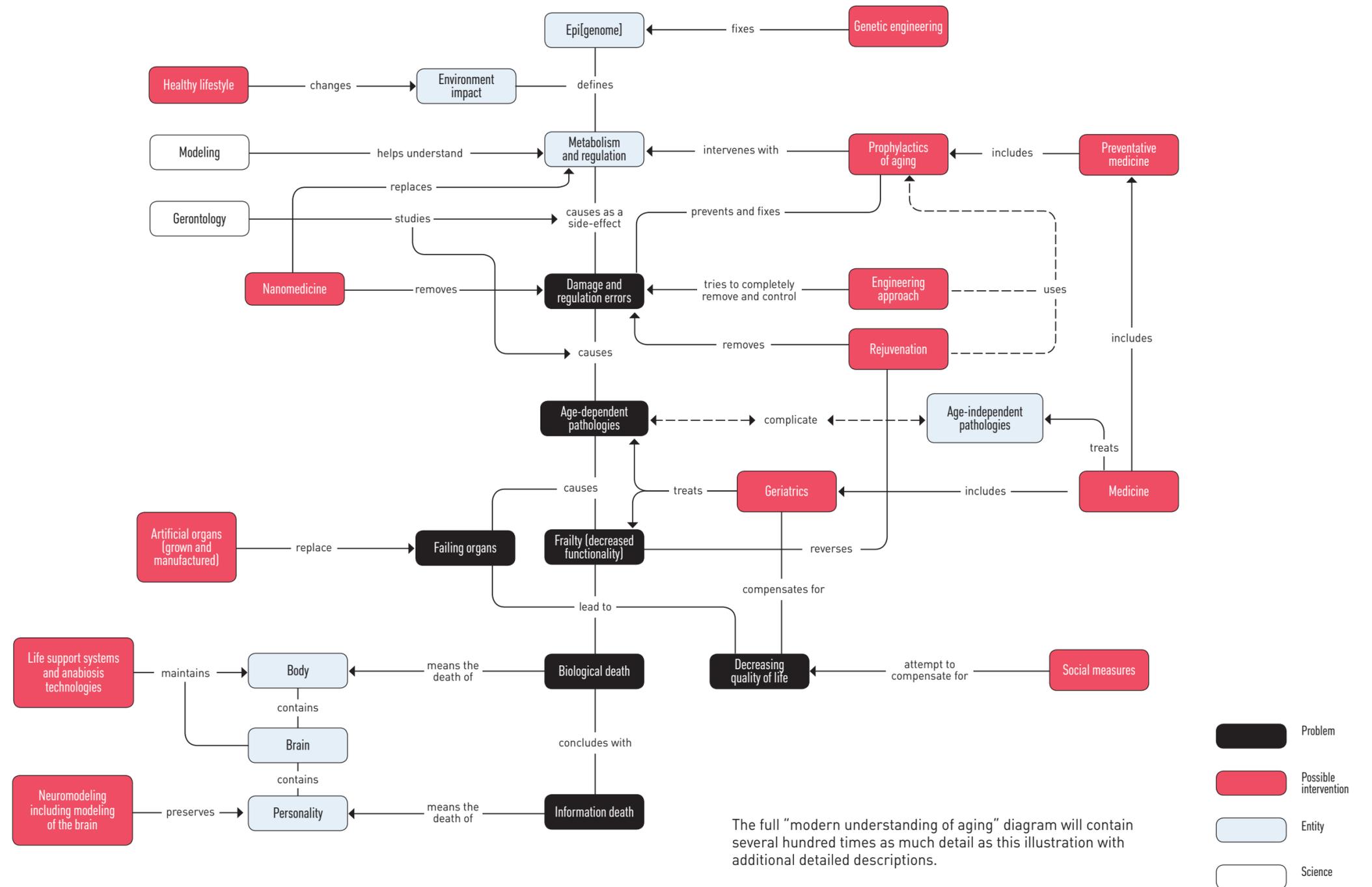
This description will make it possible to communicate our vision of the project to our partners and experts. It will also help attract potential new participants in the project.

In addition this description will serve as a starting point for development of the scientific program to eliminate aging. After outlining the modern understanding of aging we will start work on a roadmap (a concept of the program outlining key directions for research) to elimination of aging. The roadmap will be expanded and finalized at an interactive scientific conference in a “Dahlem conference” format (very effective Dahlem Konferenzen workshops were held in the Free University of Berlin since 1974). Participants at such conference will do more than just give presentations, during a whole week they will work in groups on a section of the roadmap.

The roadmap will be expanded with information about specific research projects and other information. The resulting document will contain the “scientific program to eliminate aging”. We will then lobby for it to be accepted and funded. Large scale research project will thus be initiated, culminating in the development of methods and tools to first slow and then completely eliminate human aging.

Today we want to offer one approach to developing the program to cure aging for discussion, comments and criticism. This approach has been developed by a group of Russian researchers for “Science for life Extension” foundation.

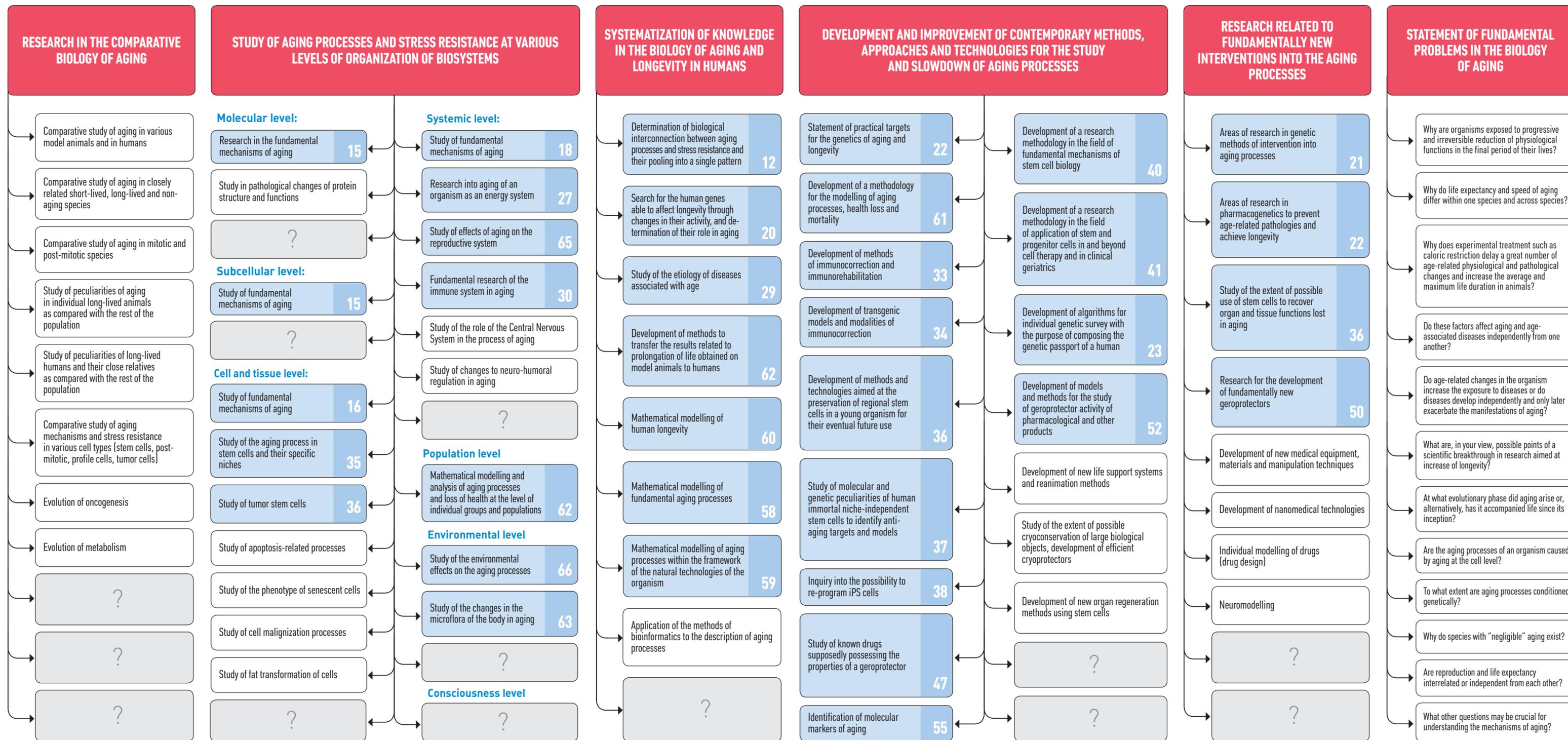
LIFE, AGING AND DEATH PROCESSES IN HUMANS. INTERVENTION POSSIBILITIES



We propose for discussion, amendment and supplement an approach to the development of the “Science against Aging” program set forth by Russian scientists. Upon completion of the development of all program sections, materials will be structured according to this suggested pattern.

STRUCTURE PROPOSAL OF THE “SCIENCE AGAINST AGING” PROGRAM

Individual proposals regarding this section are published in a booklet on the page specified.
 This section requires elaboration.
 Reserved sections for the further development of the program.



PROGRAM AIMS AND OBJECTIVES

MAIN AIM

Development and application of scientific methods in order to substantially extend human healthy lifespan

PRIORITY OBJECTIVES:

- Research in fundamental mechanisms of aging
- Development of methods for intervention in the aging process in order to slow it down
- 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

PROGRAM

SCIENCE AGAINST AGING

SELECTED PROPOSALS

Russian scientists have elaborated a number of proposals on several sections of «Science Against Aging» program.

We would appreciate if you could take part in development of these sections or contribute to working out new ones.

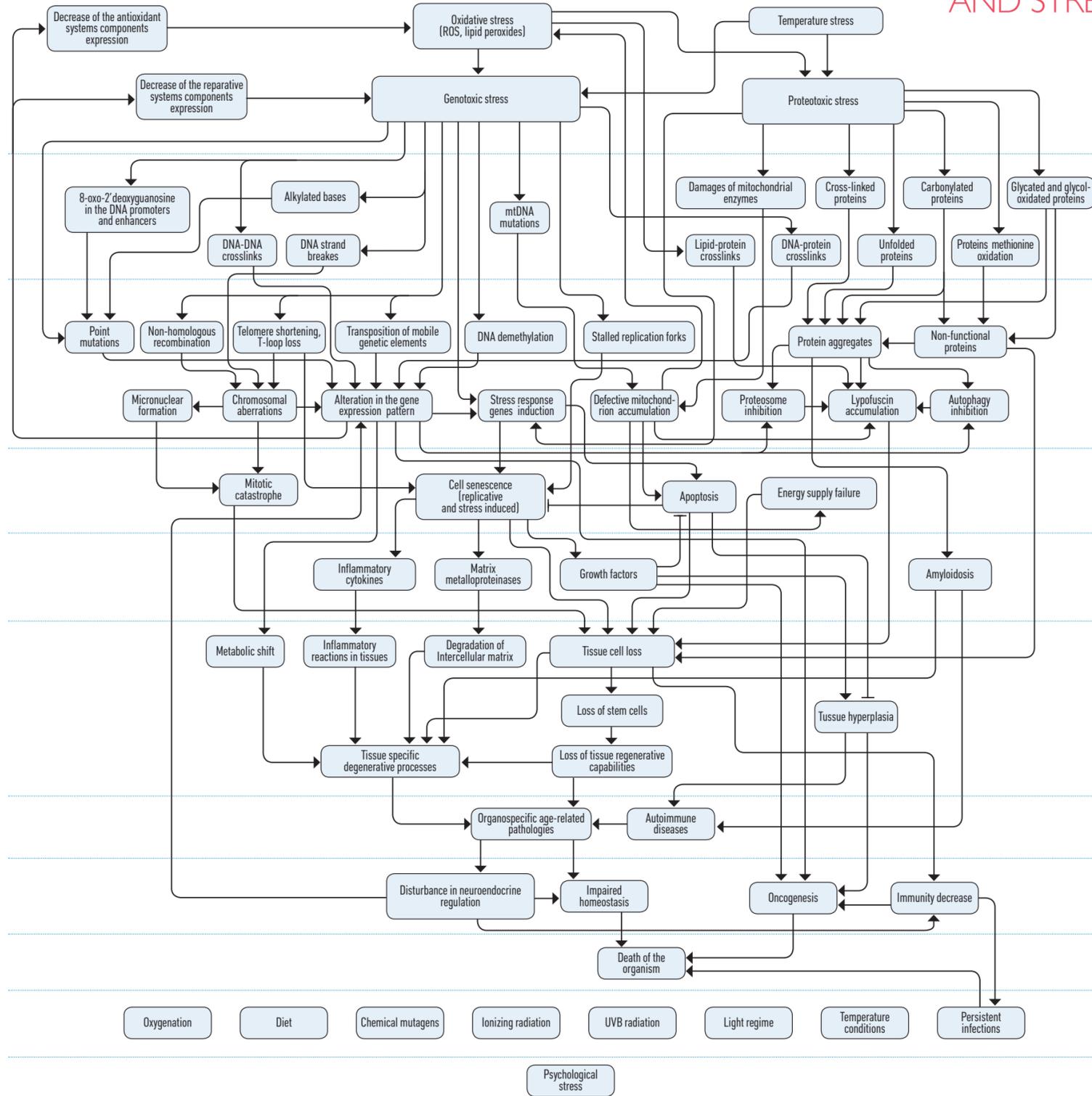
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AGING

FUNDAMENTAL MECHANISMS OF AGING AND STRESS RESISTANCE

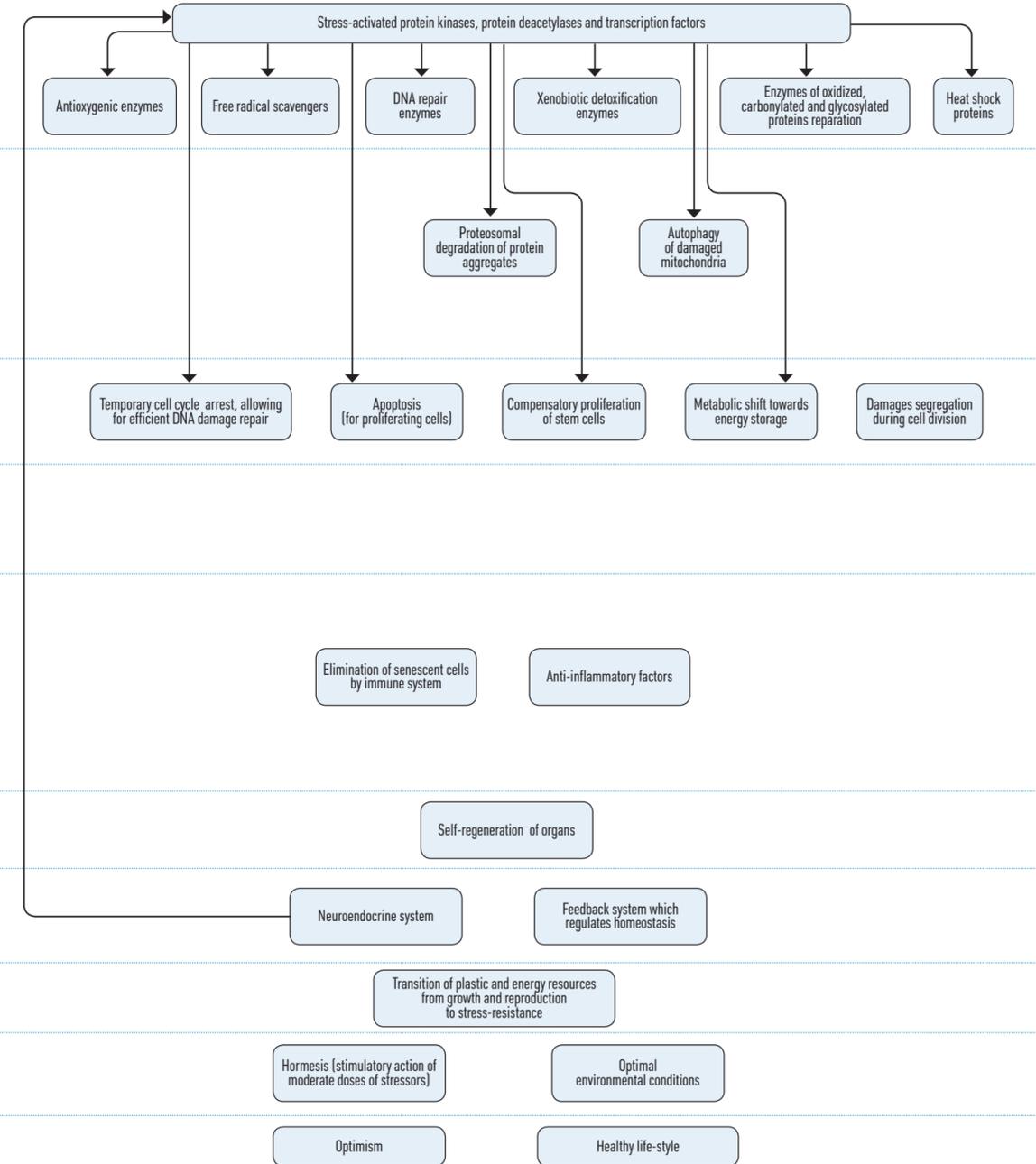
Maps of these biological dependencies will be further developed while the program "Science against aging" is developed. The understanding of these dependencies may become one of the key moments for further advancing the methods to retard aging processes in human organism.



STRESS RESISTANCE

Biosystem integration levels

- Molecular
- Subcellular
- Cellular
- Intercellular
- Tissues
- Organs
- Organ systems
- Organism
- Ecological
- Psychologic



Section 1

FUNDAMENTAL MECHANISMS OF AGING

MAIN RESEARCH AREAS

Science is gradually approaching an understanding of the basis of the aging process. Aging on the molecular (DNA, proteins and lipids modification) and cellular levels (replicative and stress-induced aging) is being investigated, as well as the role of apoptosis deregulation and the genetic instability in age-specific pathologies. However, the disparate facts available often result in contradictory conclusions being reached, and thus the contribution of different damage on the aging of a cell is constantly being reviewed.

To make these issues clear full-scale research on the molecular, sub-cellular cellular histologic, and organ levels of the entity are required, with the ultimate objective being the development of a comprehensive mathematical model of human aging which would take into account the contribution of each factor from molecules to organs. At present, there is a transition from the concept of a passive accumulation of genetic errors to the concept of identifying the regulatory epigenetic changes which influence gene expression (damage of gene promoters and enhancers, DNA demethylation and histones, compensatory stress response).

On the whole these epigenetic processes do not look spontaneous any longer since they are reproduced in one individual to another (although with allowances for differing biological ages) and often precede the age-related manifestation of any malfunction. It is very important to learn to track these age-dependent modifications for each gene within the human genome. Today, this objective can be attained due to the advent of molecular genetic methods of work with human cellular cultures, as well as the possibility of mapping out hundred-year-olds' longevity locus to

compare their gene expression with various aging and young individuals' tissues (in the brain, muscles, liver, and kidneys).

A grounded optimism appears that the approaches which have been developed so far are enough to make a human a major genetic subject in the exploration of aging mechanisms. Such research requires a full-scale program which would synchronize the separate efforts of various scientific groups who examine different aspects of aging on the molecular, sub-cellular, organ and population levels in the context of biochemical, genetic, ecological, demographical and medical research.

The availability of such a comprehensive program, covering all aspects of the aging problem, will allow one to estimate the amount of financing required for the research. Its implementation will enable us to create a mathematical model of the aging process at all the levels organization of life, to learn to assess a person's biological age (their estimated life-span) and work out a set of practical measures to slow down the aging process.

In this way, three objectives will be attained:

1. Human aging mechanisms will be explored,
2. Anti-aging medical problems will be addressed,
and
3. Methods to achieve longevity will be developed.



1.1. RESEARCH ON DIFFERENT LEVELS OF LIVING MATTER ORGANIZATION

1.1.1. MOLECULAR LEVEL

1.1.1.1. Fundamental laws of cell metabolism changes during aging:

- 1.1.1.1.1. Characterization of «vulnerable» metabolic reactions—crossing points of metabolic pathways
- 1.1.1.1.2. Stating the resistance criteria of living organism
- 1.1.1.1.3. Finding the ways to improve metabolic resistance during aging
- 1.1.1.1.4. Correlation of metabolism resistance and lability processes (biochemical adaptation mechanisms)

1.1.1.2. Studying reversible and irreversible metabolism failures during aging

- 1.1.1.2.1. Models in vitro
- 1.1.1.2.2. Development of adequate experimental in vivo models
- 1.1.1.2.3. Metabolic pathways
- 1.1.1.2.4. Studying the risk factors sensitivity threshold
- 1.1.1.2.5. Occupation-associated diseases
- 1.1.1.2.6. Sensitivity to anthropogenic factors

1.1.1.3. Development of adequate biochemical models of cell and organism senescence

- 1.1.1.3.1. Rapidly aging mice and rats under evaluating the effects of longevity factors
- 1.1.1.3.2. Prenatal hyperhomocysteinemia

1.1.1.4. Research on signaling and adaptive function of free radicals in a cell during aging

- 1.1.1.4.1. Mobilization factors (autoserotherapy, radiotherapeutics, UV, laser treatment, temperature) and basic mechanisms of their impact

1.1.1.5. Research of condition of tissues and cells antioxidant protection

- 1.1.1.5.1. Integral antioxidant potential assessment

- 1.1.1.5.2. Characterization of resistance to induced oxidation of biological structures
- 1.1.1.5.3. Development of methods for quantitative evaluation of tissue oxidative and carbonyl stress (express methods for measurement of protein carbonyls, malondialdehyde, methyl glyoxal, homocysteine and other metabolites)

1.1.1.6. Analysis of protein damage contribution to aging processes and age-dependent pathologies including:

- 1.1.1.6.1. Oxidation of amino acid protein radicals (methionine, tryptophan, histidine and other), accumulation of protein carbonyls;
- 1.1.1.6.2. Proteins cross-links;
- 1.1.1.6.3. Glycosidase activity and nonenzymatic protein glycation.

1.1.1.7. Studies of the role of spontaneous DNA damage in aging :

- 1.1.1.7.1. 8-oxo-2'-deoxyguanosine in GC-abundant promoter sites of genes;
- 1.1.1.7.2. DNA-protein and DNA-DNA cross-links.

1.1.1.8. Investigation of lipid damage in aging:

- 1.1.1.8.1. Diene conjugates;
- 1.1.1.8.2. Malondialdehyde, methyl glyoxal;
- 1.1.1.8.3. Lipofuscin (ceroid) accumulation.

1.1.2. SUBCELLULAR LEVEL:

1.1.2.1. Studies of epigenetic changes in aging cell nucleus

- 1.1.2.1.1. Structural disorders of nucleus (nuclear lamina, nucleoplasm);
- 1.1.2.1.2. Histones modifications;
- 1.1.2.1.3. Chromatin compactization

1.1.2.2. Investigation of age-related alterations in mitochondrion:

- 1.1.2.2.1. Free radicals – mtDNA damage – free radicals;
- 1.1.2.2.2. Free radicals – mt DNA damage – cell energetics disruption;

1.1.2.1.3. Homoplasma of damaged mitochondria.

1.1.2.3. Aging analysis in the context of proteolysis and autophagy systems.

1.1.2.4. Genomic instability as biomarker and possible reason of aging:

1.1.2.4.1. Telomere shortening mechanisms.

1.1.2.4.1.1. Telomerase reactivation as anti-aging factor.

1.1.2.4.2. Reasons for activation of mobile genetic elements transposition.

1.1.2.4.3. Conditions for spontaneous DNA nuclear and mitochondrion mutagenesis.

1.1.2.4.3.1. DNA repair as anti-aging factor.

1.1.2.4.4. Factors initiating chromosome aberrations:

1.1.2.4.4.1. Bridges

1.1.2.4.4.2. Fragments

1.1.2.4.4.3. Translocations

1.1.2.4.5. Reasons for aneuploidy.

1.1.2.4.6. Micronucleus

1.1.2.4.7. Factors contributing to gene expression disorder:

1.1.2.4.7.1. Oxidative damage of gene promoter sites;

1.1.2.4.7.2. Age-dependent DNA demethylation;

1.1.2.4.7.3. Age-dependent acetylation, phosphorylation, methylation, ubiquitination, chromatin histone sumoylation;

1.1.2.4.7.4. Non-coding regulatory genetic elements (enhancers, silencers, insulators) which control expression of genes associated with aging;

1.1.2.4.7.5. Expression regulators from protein group Polycomb and trithorax;

1.1.2.4.7.6. The involvement of miRNA;

1.1.2.4.7.7. mRNA alternative polyadenylation regulators;

1.1.2.4.7.8. mRNA alternative splicing regulators

1.1.3. CELLULAR-TISSUE LEVEL

1.1.3.1. Study of cell aging in interconnection with tissue regeneration and aging of the whole organism:

1.1.3.1.1. Replicative and segregative aging of proliferating somatic cells;

1.1.3.1.2. Stress induced aging of stem cells;

1.1.3.1.3. Postmitotic aging of (non-proliferating) cells.

1.1.3.2. Identification of the role of apoptosis in aging of an organism (ways for tissue-specific apoptosis deregulation):

1.1.3.2.1. Reasons of higher hypersensitivity to apoptosis with age in some cell types:

1.1.3.2.1.2. neurons;

1.1.3.2.1.3. cardiomyocytes;

1.1.3.2.1.4. somatic muscle cells;

1.1.3.2.1.5. leukocytes (T-cells, polymorphonucleocytes);

1.1.3.2.1.6. neutrophils;

1.1.3.2.1.7. megakaryocytes;

1.1.3.2.1.8. renal cells;

1.1.3.2.1.9. endotheliocytes;

1.1.3.2.1.10. chondrocytes;

1.1.3.2.2. Mechanisms of age-related decrease in liability to apoptosis with age in some type of cells:

1.1.3.2.2.1. large intestine cells;

1.1.3.2.2.2. fibroblasts;

1.1.3.2.2.3. hepatocytes.

1.1.3.3. Study of apoptosis regulation for «anti-aging»:

1.1.3.3.1. Studies of the possibilities of apoptosis induction in cells with weakening repair capacity and compensatory proliferation of steady cells at early developmental stages for deceleration of subsequent tissues aging

1.1.3.3.2. Development of age-dependent apoptosis inhibition methods in postmitotic or weakly proliferating tissues

1.1.3.4. Cytodifferentiation and dedifferentiation regulation for modification of the rate of aging :

1.1.3.4.1. Study of of replicative aging as a possible result of terminal differentiation of cells

1.1.3.4.2. Search of regulatory structures postulated by Olovnikov's redosome theory and analysis of their possible contribution to differentiation, morphogenesis and aging processes

1.1.3.4.3. Study of cytodifferentiation of radial glia to astrocytes as a possible cause of postmitotic brain and aging of mammals

1.1.3.5. Regulation of cell proliferation and regeneration

1.1.3.6. Study of regulatory effect of neuropeptides and natural modulators in nervous and immune system function modification during aging and cell function regulation with the help of specific receptors:

1.1.3.6.1. The role of glutamate receptors in transneuronal function modulation

1.1.3.6.2. Role of cannabinoid receptors in aging resistance

1.1.3.6.3. The influence of endorphins on age-related changes in memory function

1.1.3.6.4. Investigating the effects of carnosine and its derivatives as natural geroprotectors:

1.1.3.6.4.1. Hyperhomocysteinemia protection

1.1.3.6.4.2. Counteraction for excitotoxic mechanisms of oxidative stress

1.1.3.6.4.3. Interdiction of neurodegenerative changes development in brain neurons

1.1.3.6.4.4. Tissue repair processes recovery

1.1.3.6.4.5. Regulation of immunocompetent system functions

1.1.3.7. Search for natural metabolites of animal origin, that delay aging:

1.1.3.7.1. Pharmacology of natural modulators of animal origin

1.1.3.8. Study of resistance to environmental factors

1.1.3.8.1. Biochemical resistance reserves (chaperones, adaptogens)

1.1.3.8.2. Study of natural factors of biochemical tolerance

1.1.3.9. Specific metabolic features of centenarians:

1.1.3.9.1. Research on resistance mechanisms of blood cells

1.1.3.9.2. Study of haemodynamics

1.1.3.9.3. Lymphocytes with atypical markers

1.1.3.9.4. Epidemiological surveys on biologically active factors of metabolism

1.1.3.10. Longevity without diseases :

1.2.3.10.1. Biochemical mechanisms of cellular genome stabilization

1.2.3.10.2. Complex approaches to treatment of age-related diseases

1.1.4. SYSTEM LEVEL

1.1.4.1. Study of malfunction related to neuroendocrinal function:

1.1.4.1.1. Functions of hypothalamus:

1.1.4.1.1.1. circadian rhythms

1.1.4.1.1.2. Dilman's ontogenetic clock

1.1.4.1.2. insulin signaling as a mechanism of:

1.1.4.1.2.1. type II diabetes

1.1.4.1.2.2. Increasing of fat/muscle ratio

1.1.4.1.3. Functions of epiphysis:

1.1.4.1.3.1. production and cycle of melatonin

1.1.4.1.3.2. peptide production

1.1.4.1.4. Functions of steroid sex hormones as the cause of:

1.1.4.1.4.1. Climax

1.1.4.1.4.2. Sexual disfunction

1.1.4.2. Study of the reasons for age-related immunity disorders which result in:

1.1.4.2.1. Susceptibility to infection

1.1.4.2.2. Autoimmune diseases (rheumatoid arthritis and other)



1.1.4.2.3. Proneness to tumorigenesis

1.1.4.3. Study of reproductive performance abnormality:

1.1.4.3.1. Teratogenesis in fetus

1.1.4.3.2. Impotence

1.1.4.5. Age-dependent oncogenesis

1.1.4.6. Analysis of mechanisms of premature aging syndromes:

1.1.4.6.1. Werner syndrome

1.1.4.6.2. Hutchinson-Gilford syndrome

1.1.4.6.3. Cockayne syndrome

1.1.4.6.4. Ataxia-teleangiectasia

1.1.4.6.5. Xeroderma pigmentosum

1.1.4.6.6. Falconi's Anaemia

1.1.4.6.7. Rothmund-Thomson syndrome

1.1.4.6.8. Bloom syndrome

1.1.4.6.9. Nijmegen Breakage Syndrome

1.1.4.6.10. Trichothiodystrophy

1.1.4.6.11. Congenital diskertosis

1.1.4.7. Search of aging biomarkers:

1.1.4.7.1. Biological age markers,

1.1.4.7.2. Longevity predictors.

Section 2

GENETICS OF LIFESPAN AND AGING

MAIN RESEARCH DIRECTIONS

At present the most successful and encouraging aspect of the studies is the search for longevity genes in animal models (nematodes, fruit flies, mice etc). It is due to the discovery of long-lived mutants that the present-day stage of gerontology development has been marked by an alteration of the scientific paradigm of aging from that of being a passive mechanical running down to an idea of it being a set of regulatory epigenetic modifications which determine the age-related expression dynamics for certain evolutionary conservative gene groups .

The attainment has included a tenfold lifespan extension in nematode and yeast cells in 2008, and a twofold one for fruit flies and mice. The following promising areas can be indicated in this aspect: The discovery of new longevity genes in various models (screening of deletions, hypomorphic mutations and over-expression of genes causing longevity, and also QTL analysis).

Proof of the evolutionary conservative role of the longevity gene orthologs (the search for longevity genes, similar to the ones discovered in yeast and nematodes, fruit flies and mice). Such evidence for forms more similar to human, but long-lived models, (mice and rats) requires the application of (and development of new) biomarkers in various age groups, as conventional survival tests for these animals are unreasonably long. Confirmation that allelic variants of the newly discovered gerontogenes' orthologs have an association with family longevity in humans (through a population genetic analysis of 90 to 100-year-old individuals). As is known, many genes encode enzymes which participate in a cell's life, e.g. facilitate metabolism, breathing, chemical synthesis, and these enzymes can be regulated pharmacologically. Our objective

is to select a substance (future drugs) which would exactly regulate the enzymes encoded by the longevity genes known to us. Thus, genetic methods will develop at a new, pharmacologic level (pharmacogenetics).

The immediate problems of aging and longevity genetics are the following:

- further study in comparative aging genetics;
- the search for effective biomarkers of aging;
- identification of genetic mechanisms, actions which slow down aging, pharmacologic drugs and biological additives;
- longevity and age-dependent genes' polymorphism analysis;
- Identification of genetic networks conditioning extra-environmental mechanisms on the impact on lifespan (caloric content of food, light conditions etc.). Apparently, the maximum lifespan extension can be attained by simultaneous regulation of (with genetic and pharmacological methods) several genetic networks which control lifespan. The «Geronogene's» functioning mechanisms study carried out on animal models will help establish the approaches towards human lifespan extension, as well as making it more qualitative, and free of age-related pathologies. This objective determines the following practical tasks for lifespan genetics.

2.1. IDENTIFYING GENES OF LONGEVITY

2.1.1. In cell culture experiments:

- 2.1.1.1. In yeast cell culture model:
 - 2.1.1.1.1. Replicative longevity;
 - 2.1.1.1.2. Chronological longevity.
- 2.1.1.2. In mammal and human cell cultures:
 - 2.1.1.2.1. Replicative lifespan;
 - 2.1.1.2.2. Survivability of cells in stationary phase.

2.1.2. In model animals in vivo:

- 2.1.2.1. QTL analysis;
- 2.1.2.2. Hypomorphic mutations;
- 2.1.2.3. Deletions;
- 2.1.2.4. Overexpression.

2.1.3. Comparative aging biology In living organisms with negligible senescence:

- 2.1.3.1. Age-related dynamics of gene expression in various tissues of the following species:
 - 2.1.3.1.1. *Strongylocentrotus franciscanus* (red sea-urchin)
 - 2.1.3.1.2. *Homarus americanus* (American lobster)
 - 2.1.3.1.3. *Arctica islandica* (Icelandic cyprine)
 - 2.1.3.1.4. *Sebastes aleutianus* (roughey rockfish)
 - 2.1.3.1.5. *Hoplostethus atlanticus* (Orange roughy)
 - 2.1.3.1.6. *Alloctytus verrucosus* (Warty oreo)
 - 2.1.3.1.7. *Acipenser fulvescens* (Lake sturgeon)
 - 2.1.3.1.8. *Bufo americanus* (American Toad)
 - 2.1.3.1.9. *Geochelone nigra* (Galapagos giant tortoise)
 - 2.1.3.1.10. *G. gigantea* (giant land tortoise)
 - 2.1.3.1.11. *Terrapene carolina* (Eastern Box Turtle)

- 2.1.3.1.12. *Emydoidea blandingii* (Blanding's Turtle)
- 2.1.3.1.13. *Chrysemys picta* (Painted Turtle)
- 2.1.3.1.14. *Heterocephalus glaber* (naked mole rat)
- 2.1.3.1.15. Long-lived females of social insects (bees, termites, wasps, ants)
- 2.1.3.1.16. *Pinus longaeva* (Great Basin Bristlecone Pine)
- 2.1.3.1.17. *Sequoiadendron giganteum* (Giant Sequoia)

2.1.3.2. Activity comparison for longevity genes of species with alternative ontogenesis forms:

- 2.1.3.2.1. Workers and females of social insects
- 2.1.3.2.2. Free-living and parasitic forms of nematode worms *Strongyloides ratti*.
- 2.1.3.2.3. Reproductive and diapause forms of *C. elegans*.
- 2.1.3.2.4. Seasonal forms of *Bicyclus anynana* butterfly.

2.1.4. In human :

- 2.1.4.1. Research into single nucleotide polymorphisms in groups of people with different lifespan.
- 2.1.4.2. Longitudinal (long-term) research of siblings pairs (close relatives) of middle age, discordant (differing), or concordant (similar) in various physiological functions slowdown rate followed by comparison of the findings with the data about the investigated individuals' longevity.
- 2.1.4.3. Mapping of longevity locuses of long-lived family members.
- 2.1.4.4. Search of alleles, involved in longevity (90-100 years).
- 2.1.4.5. Gene expression comparison of various tissues (brain, muscles, liver, kidneys) of aging and young Individuals in order to find genes conditioning tissue-specific aging.

2.2 ANALYSIS OF THE EVOLUTION-CONSERVATIVE ROLE IN HUMANS OF LONGEVITY GENES DISCOVERED IN MODEL ANIMALS

2.2.1. Genes-regulators of ontogenetic programs (sensing and transduction of exogenous and endogenous signals), involved in signaling of the following:

- 2.2.1.1. insulin/IGF-1;
- 2.2.1.2. growth hormone;
- 2.2.1.3. Klotho;
- 2.2.1.4. Lipophilic (thyroid and steroid) hormones.

2.2.2. Genes-mediators of stress resistance:

- 2.2.2.1. Phosphoinositol-3-kinase;
- 2.2.2.2. TOR-kinase;
- 2.2.2.3. serine / threonine protein kinase;
- 2.2.2.4. PTEN phosphatases;
- 2.2.2.5. deacetylases of sirtuin family;
- 2.2.2.6. JNK protein kinase;
- 2.2.2.7. MST-1 protein kinase;
- 2.2.2.8. Nrf2/ SKN-1 transcription factor;
- 2.2.2.9. FOXO transcription factor;
- 2.2.2.10. HSF-1 transcription factor.
- 2.2.2.11. NF-kB transcription factor.

2.2.3. Genes effectors of stress resistance:

- 2.2.3.1. superoxide dismutase;
- 2.2.3.2. catalase;
- 2.2.3.3. methionine-R-sulfoxidereductase;
- 2.2.3.4. heat-shock proteins;
- 2.2.3.5. proteasome components;
- 2.2.3.6. autophagy proteins;
- 2.2.3.7. innate immunity proteins;
- 2.2.3.8. xenobiotic detoxification factors;
- 2.2.3.9. DNA repair enzymes.

2.2.4. Genes of cell's «viability», controlling «constitutive genes»:

- 2.2.4.1. GATA-transcription factors

2.2.5. Oncosuppressors and apoptosis regulatory genes:

- 2.2.5.1. p53
- 2.2.5.2. pRB
- 2.2.5.3. p21
- 2.2.5.4. p16^{Ink4a}
- 2.2.5.5. p19^{Arf}

2.2.6. Genes involved in mitochondria functioning:

- 2.2.6.1. Electron transport chain element coding genes;
- 2.2.6.2. Tricarboxylic acids cycle enzyme genes;
- 2.2.6.3. Genes of decoupling proteins;
- 2.2.6.4. Genes of polymerase mitochondrial DNA;
- 2.2.6.5. Genes governing mitochondrial-nuclear relationship;
- 2.2.6.6. mtDNA genes.

2.3. GENETIC METHODS OF INTERVENTION IN AGING PROCESSES

2.3.1. Correction of unfavorable alleles by gene-engineering methods.

2.3.2. Search of aging associated genes activity regulation methods:

- 2.3.2.1. Changes of DNA methylation sites in such genes;
- 2.3.2.2. Alteration of covalent modification of histones [acetylations, deacetylations, etc.];
- 2.3.2.3. The RNA interference;
- 2.3.2.4. Control of alternative splicing and polyadenylation.

2.3.3. Tissue-specific correction of age-dependent changes in gene expression:

- 2.3.3.1. in CNS;
- 2.3.3.2. in liver;
- 2.3.3.3. in pancreas;
- 2.3.3.4. in kidneys;
- 2.3.3.5. in heart;
- 2.3.3.6. in vessels;
- 2.3.3.7. in other vital organs.

2.3.4. Differentiated cells nucleus reprogramming in order to recover pluripotent stem cell properties.

2.3.5. Correction of changes predisposing to cellular senescence:

2.3.5.1. Telomerase reactivation in proliferative cells with simultaneous stimulation of normal p53 or other oncosuppressor activity.

2.3.6. Stimulation of cell self-repair mechanisms at an old age:

2.3.6.1. Antioxidant protection genes

2.3.6.2. Genes of DNA repair

2.3.6.3. Detoxification genes

2.3.6.4. Heat shock proteins

2.3.6.5. Autophagy genes

2.3.6.6. Proteosome genes

2.3.6.7. Sirtuins

2.3.6.8. GATA-transcription factors

2.3.6.9. FOXO transcription factors

2.3.6.10. Adenosine monophosphate – dependent kinase

2.4. RESEARCH TRENDS IN THE FIELD OF PHARMACOGENETICS OF AGING AND LONGEVITY

2.4.1. Search of geroprotectors, reducing the risk of age-dependent diseases and contributing to radical life extension as well as studying their action mechanisms:

2.4.1.1. Adaptogenes

2.4.1.2. Bioregulators:

2.4.1.2.1. Peptide bioregulators (Epitalone, Vilone, etc.)

2.4.1.2.2. Oligopeptides

2.4.1.2.3. Melatonin

2.4.1.2.4. Carnosine

2.4.1.2.5. Phitoecdosteroids

2.4.1.2.6. New bioregulators on the ground of natural compounds and their synthetic analogues.

2.4.1.3. Antioxidants:

2.4.1.3.1. Natural polyphenols and flavonoids (Resveratrol, Lignans, Curcumin, Quercetin, Silimarin);

2.4.1.3.2. Skulachev ions;

2.4.1.3.3. New antioxidants on the basis of natural compounds and their synthetic analogues (Interceptors of free radicals or stimulators of detoxication genes expression);

2.4.1.4. Mechanisms of substitute hormonal therapy.

2.4.1.5. The compounds influencing mechanisms involved in aging processes:

2.4.1.5.1. Low-molecular regulators search;

2.4.1.5.2. Peptide development, blocking certain enzymes ("synthetic" mutations).

2.4.1.6. Hormetines (inductors of moderated stress-answer with the purpose of protective systems training).

2.5. PRACTICAL TASKS OF AGING GENETICS AND LONGEVITY

2.5.1. Screening human longevity genes:

2.5.1.1. Drawing databases of animal longevity genes, having human genes-analogues.

2.5.1.2. Cataloguing of loci and allelic genes variants, providing family longevity of a person (90 years and more). SNP-analysis.

2.5.1.3. Cataloguing polymorphisms, associated with specific age-dependent diseases.

2.5.1.4. Creation of database, reflecting general and tissue-specific age-dependent dynamics of genes activity.

2.5.1.5. Reproduced age-dependant epigenetic changes mapping (DNA methylation, histone code change), for each gene and regulator element of various human tissues.

2.5.2. Screening of genetic aging biomarkers
Analysis of genes expression in separate tissues of an individual on microchips in order to :

- 2.5.2.1. Reveal latent aging stages, preceding to obvious functional infringements.
- 2.5.2.2. Predict lifespan (detection of biological age).
- 2.5.2.3. Choose the necessary procedures for correction of age-dependent alterations in gene expression.

2.5.3. Regulation of human longevity genes:

- 2.5.3.1. Reprogramming of genomes of certain types of differentiated cells in order to return to them the properties of pluripotent stem cells in vivo.
- 2.5.3.2. Creation of technological approaches for selection and elimination of weakened (quickly growing old) variants of cells and stimulation of compensatory proliferation of steady variants.
- 2.5.3.3. Telomerase reactivation in cells predisposed to replicative aging, against the background of increased activity of normal variants of p53; p16 or ARF.
- 2.5.3.4. Working out ways of tissue-specific administration of certain longevity gene alleles (by means of genetic vectors of retrovirus or other nature).
- 2.5.3.5. Correction of longevity unfavourable alleles:
 - 2.5.3.5.1. targeted mutagenesis of these genes (for example induction of hypomorphic or dominant - negative somatic mutations);
 - 2.5.3.5.2. enhancers regulation (including tissue-specific);
 - 2.5.3.5.3. RNA-interference of their products.
- 2.5.3.6. Obtaining pharmacological regulators of life expectancy genes expression.
- 2.5.3.7. Search for low-molecular substances capable of targeted modification of the activity of proteins coded by lifespan genes.
- 2.5.3.8. Creation of specific regulative peptide inhibitors for proteins, coded by lifespan genes (induction of "synthetic mutations").
- 2.5.3.9. Development of technological approaches for tissue-specific gene expression regulation in general (change of a DNA methylation degree,

histone modification, regulation of alternative splicing, polyadenylation, RNA- interference).

- 2.5.3.10. Tissue-specific regulation of cellular senescence genes activity (p21, p16, ARF).
- 2.5.3.11. Search for correction methods of age-dependent changes of gene expression by means of a diet and optimization of environmental conditions (physical and mental load, light and temperature modes).

2.6 DEVELOPMENT OF THE INDIVIDUAL GENETIC EXAMINATION ALGORITHM (CREATION OF HUMAN GENETIC PASSPORT)

2.6.1. Development of nanochips for longevity candidate genes identification and research of alleles for the most frequent chronic diseases (osteoporosis, bronchial asthma, trombophiliya, hypertension, diabetes, adiposity, atherosclerosis, chronic illnesses of lungs, etc.):

- 2.6.1.1. Creation of a DNA collection from patients with the most serious hereditary diseases (not less than 2000 samples on one disease) and representative groups of obviously healthy individuals (not less than 1000).
- 2.6.1.2. Carrying out identification of all candidate genes and anonymous genetic loci corresponding illnesses by general genomic screening of allelic associations, according to technology HapMap in combination with SNP (single-nucleotide replacements) hybridization chips of high density.
- 2.6.1.3. Development of diagnostic biochips on the basis of obtained data convenient for mass diagnostics of hereditary predispositions to heavy chronic diseases—principal causes of disablement and reduction of the human life expectancy.

2.6.2. General genome search for longevity candidate genes, as well as comparative population

analysis of frequency dynamics for such rare (functionally defective) alleles of genes of cardiovascular and bone systems, and also genes of detoxification system, blood coagulation, lipid and carbohydrate exchange systems in different age groups, including newborns and individuals of senior age:

- 2.6.2.1. Creation of a collection of DNA samples of long-livers, middle-aged subjects and newborns (about 1000 samples in each group).
- 2.6.2.2. Comparison between genetic profiles of subjects of different age in order to identify new candidate genes and anonymous DNA locuses associated with longevity.
- 2.6.2.3. Comparison of identified longevity genes with similar genes in other mammals.
- 2.6.2.4. Elaboration, using biological models, of the methods for targeted regulation of longevity gene expression with the help of geroprotectors food supplements and genetic therapy techniques.

2.6.3. Comparison of the main biochemical and functional parameters of organs and tissues with expressional activity of polymorphic gene variants of corresponding systems of life-support in cases of healthy Individuals and patients with various frequent chronic diseases:

- 2.6.3.1. Elaboration of the analysis techniques for expression profiles of longevity genes and disease genes in various tissues from long-livers and patients with chronic diseases.
- 2.6.3.2. Comparison of expression profiles of the studied candidate genes versus findings of biochemical, physiological and other laboratory tests in order to clarify genotype/phenotype interrelation and obtaining objective criteria for identification of a weak metabolic link in the examined subjects.

2.6.4. Development of complex parameters (genetic, biochemical, functional) for evaluation of different organs, tissues and systems biological age:

- 2.6.4.1. Experimental development of evaluation parameters on biological models;
- 2.6.4.2. Working out the scheme of the complex (medicinal, food, gene-engineering) corrections of weak metabolic functions.

2.6.5. Development of individual examination algorithms, allowing to combine individual genome features with already known approaches and methods of life extension and active longevity (caloric restriction full-valued individual diet, anti-stress therapy, fitness and sport).

2.6.6. Nanochip development (on the basis of genetic testing results and pharmacogenetics data) for testings of individual sensitivity features to some drugs, including to geroprotectors and food supplements in order to choose the optimal therapeutic dose and achieve maximal lifespan.

2.6.7. Carrying out comparative retrospective and prospective analysis of genetic testing for hereditary predispositions of newborns in families with high risk of frequent multifactorial illnesses (bronchial asthma, diabetes, adiposity, etc.):

- 2.6.7.1. Creation of genetic passport for a newborn (based on findings of retrospective genetic studies in patients with severe multifactorial diseases);
- 2.6.7.2. Early presymptomatic detection of children with hereditary predisposition to multifactorial illnesses (based on prospective genetic analysis in high-risk families for a particular pathology) with the purpose of preventive maintenance of chronic diseases.

2.6.8. Creation of the centenarian genetic passport:

- 2.6.8.1. Experimental development,
- 2.6.8.2. Clarification through clinical trials;
- 2.6.8.3. Evaluation of the possibility of rendering targeted effect on longevity

gene and aging gene expression with geroprotectors, food supplements (oligopeptides), hormones as well as gene regulation techniques (interference RNA) in order to achieve maximal lifespan.

2.6.9. Creation of a generalized genetic health and longevity passport, combining the findings of tests for hereditary propensity to multifactorial diseases and aging and longevity gene test results (using the bio-IT methods and computer programming).

2.6.10. Development of a computer-assisted individual genetic active longevity and maximal lifespan program on the basis of the generalized genetic health and longevity passport.

Section 3

METABOLIC ASPECTS OF AGING AND LONGEVITY

MAIN RESEARCH DIRECTIONS

With age the consumption of oxygen in cells decreases. This is a well established fact. Still, why does this occur? To answer this question one needs integrated research. It is clear, that a decrease in oxygen consumption is the result of certain processes developing in an organism with age. The reasons for that are:

- structural and functional restructuring of the mitochondria,
- reduction of mitochondrial oxidation due to other causes;
- the aging of red blood cells (a decrease in their renewal rate) – the cause is the dysfunction of spinal medulla or erythropoiesis dysfunction (the maturation of red blood cells from precursor cells);
- possible compensatory response is an increase in oxygen reactive species production outside the mitochondria, as they act as an additional source of energy. Thereupon, it is necessary to consider age-related oxidative stress as a form of adaptation;
- energy substrates (glucose and fatty acids) are oxidized by oxygen in the mitochondria (aerobic oxidation), if oxidation is decreasing, the consumption of these substrates is also decreasing. However, a converse result is also possible;
- strengthening the role of peroxisomes (peroxide oxidation), which oxidize fatty acids by oxygen in addition to mitochondria. It is an adaptive reaction as well, but in this case it acts as a reaction to an excess of fatty acids in the cell.

It has been suggested that it is the excess of energy substrate such as fatty acids in the pericellular space that leads to all these changes. This excess is a result of aging. It leads to changes in the internal environment of an organism, to which the organism begins to adapt. Oxidative stress and reduced oxygen

consumption are adaptive mechanisms due to which the organism adapts to new homeostatic conditions.

In the process of aging there arises a dysfunction in the homeostasis of glucose and fatty acids. This is well known. Yet, we may ask why this is happening? The dysfunction of glucose homeostasis is the cause for the development of diabetes in older people (diabetes type 2). The dysfunction of the homeostasis of fatty acids leads to the adipose degeneration of tissue. What is the cause for the dysfunction of homeostasis in these substrates? If scientists find an answer to this question, the cause of aging of any organism as a functional self-renewing system will be stated.

To do so, it is necessary to examine:

1. Genes regulating the metabolism of energy substrates. To identify their interrelationship, and their means to create a genetic network.
2. The mechanisms for the distribution of substrates and a preservation of their homeostasis overlaying metabolic scheme over the genetic network.
3. Age-related dysfunction of adipose tissue.
4. The metabolism of cholesterol which is closely related to metabolism of energy substrates.
5. The effect of changes in the metabolism of energy substrates on the reproductive function.
6. The study of interrelationships in the chain: dysfunction of (lack of) homeostasis of fatty acids – oxidative stress – disappearance of the reproductive function – hypercholesterolemia and insulin resistance (the development of pathological processes or adaptation) – the end of information system operation – death.

For a comprehensive study of these processes there should be a large-scale research program.



3.1. MAIN AREAS OF RESEARCH OF ORGANISM AGING AS AN ENERGY SYSTEM

3.1.1. Investigation of the reasons for reduced oxygen consumption with age

- 3.1.1.1. Study of oxygen consumption at the cellular level:
 - 3.1.1.1.1. Analysis of structural and functional changes in mitochondria:
 - 3.1.1.1.1.1. Alterations of mitochondrial genome;
 - 3.1.1.1.1.2. Alterations of the respiratory chain;
 - 3.1.1.1.1.3. Changes related to cell nucleus;
 - 3.1.1.1.1.4. Proliferation of mitochondria.
 - 3.1.1.1.2. Study of extramitochondrial oxidation:
 - 3.1.1.1.2.1. Peroxyoms, their formation and functions;
 - 3.1.1.1.2.2. Cytoplasmic oxidases;
 - 3.1.1.1.2.3. The regulation system of antioxidant protection
 - 3.1.1.1.2.4. Active oxygen species as an additional energy source
- 3.1.1.2. Study of oxygen consumption at the organism level:
 - 3.1.1.2.1. Development of methods to assess the degree of tissue oxygenation at rest and during physical activity;
 - 3.1.1.2.2. Development of methods to assess the level of consumption of energy substrates at rest and during physical activity;
 - 3.1.1.2.3. Determination of physical stress age limit.

3.1.2. Investigation of age-dependent changes of substrate homeostasis

- 3.1.2.1. Investigation of the role of hypothalamus in collapse of fatty acids homeostasis-Investigation of age-dependent disorders in the APUD system
- 3.1.2.2. Study of age-related changes in functioning of adipose tissue as an endocrine organ.
- 3.1.2.3. Study of changes in the internal medium of the organism in the

process of aging, its connection with hormonal disregulation

- 3.1.2.4. Study of the causes of age-related stress, its effects and adaptation mechanisms

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

- 3.1.3.1. Studying the age-dependant oxidative stress;
 - 3.1.3.1.1. Lipotoxicity as the consequence of fatty acids homeostasis failure:
 - 3.1.3.1.1.1. Lipofuscin synthesis;
 - 3.1.3.1.1.2. Protein synthesis reduction;
 - 3.1.3.1.1.3. Apoptosis;
 - 3.1.3.1.1.4. Cell dedifferentiation;
 - 3.1.3.1.1.5. Differentiation as an adipose-related phenotype.
 - 3.1.3.1.2. Glucosetoxicity as the consequence of glucose homeostasis failure:
 - 3.1.3.1.2.1. Extracellular proteins glycozilation;
 - 3.1.3.1.2.2. Skin aging;
 - 3.1.3.1.2.3. Lens aging;
 - 3.1.3.1.2.4. Neuron apoptosis;
 - 3.1.3.1.2.5. Amyloidosis.
- 3.1.3.2. Age-related hypercholesterolemia:
 - 3.1.3.2.1. Cytoplasm membrane structure changes
 - 3.1.3.2.2. Raft structure and function alterations
 - 3.1.3.2.3. Receptor sensitivity decrease
- 3.1.3.3. Age-related and alimentary hyperhomocysteinemia:
 - 3.1.3.3.1. Impact on specific receptors in the neural and immune systems;
 - 3.1.3.3.2. Toxicity mechanisms;
 - 3.1.3.3.3. Compensatory methods

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

- 3.1.4.1. Research of glucose and fatty acid distribution mechanisms in the organism:
 - 3.1.4.1.1. Investigation of glucose and fatty acids homeostasis support system and causes of its age-related failure;
 - 3.1.4.1.2. Study of relationship between metabolic and gene networks;
 - 3.1.4.1.3. Study of the role of metabolites as regulators of gene expression;
 - 3.1.4.1.4. Identification of genes responsible for glucose and fatty acid homeostasis support and their influence on longevity
- 3.1.4.2. Exploring the causes of age-dependent fat amount increase in humans:
 - 3.1.4.2.1. Studying the role of fatty acids in proliferation, differentiation and apoptosis;
 - 3.1.4.2.2. Structure-functional analysis of changes in adipose tissue;
 - 3.1.4.2.3. Studying the "Metabolic knot" functioning (adipose tissue, muscle, liver) and its changes in ontogenesis;
 - 3.1.4.2.4. Studying the mechanisms of age-related fatty transformation of non- adipose tissues.

3.2. RESEARCH ON FACTORS REGULATING LONGEVITY OF AN ORGANISM AS A SYSTEM

3.2.1. Environmental physical factors:

- 3.2.1.1. Illumination;
- 3.2.1.2. Ionizing radiation;
- 3.2.1.3. Temperature;
- 3.2.1.4. Microelements;
- 3.2.1.5. Pollutants;
- 3.2.1.6. Landscape factors;
- 3.2.1.7. Climate.

3.2.2. Social factors:

- 3.2.2.1. Poverty;

- 3.2.2.2. Living conditions;
- 3.2.2.3. Working conditions;
- 3.2.2.4. Social stresses.

3.2.3. Food resources («mono-nutrition»):

- 3.2.3.1. Seafood and fish (poly-unsaturated fatty acids);
- 3.2.3.2. Red wine (polyphenols);
- 3.2.3.3. Olive oil (oleic acid);
- 3.2.3.4. Cruciferers (antioxidants);
- 3.2.3.5. Apples (pectin).

3.2.4. Caloric restriction:

- 3.2.4.1. Vegeterians;
- 3.2.4.2. Total non-fat diet;
- 3.2.4.3. Saturated fat-free diet;
- 3.2.4.4. Slowly digested carbohydrates.

3.2.5. Metabolic processes retardation:

- 3.2.5.1. Hypobiosis;
- 3.2.5.2. Lethargy.

3.3. STUDYING THE METABOLIC CAUSES OF REPRODUCTION DECREASE

3.3.1. Exploring the association between glucose and fatty acids metabolism and cholesterol metabolism:

- 3.3.1.1. Hepatic steatosis and atherosclerosis;
- 3.3.1.2. Gallbladder cholesterosis;
- 3.3.1.3. Insulin resistance and atherosclerosis;
- 3.3.1.4. Gender-specific metabolism of cholesterol;
- 3.3.1.5. Lipid metabolism and synthesis of sex hormones.

3.3.2. Studying the role of sex hormones in energy substrate metabolism:

- 3.3.2.1. Estrogen and adipose tissue;
- 3.3.2.2. Androgens and muscle tissue.

3.3.3. Studying the role of sex hormones in energy substrate metabolism:

3.3.3.1. Metabolic characteristics in women in pre-and postmenopausal period;

3.3.3.2. Male senescence.

3.4. STUDYING THE AGE-ASSOCIATED DISEASE ETIOLOGY

3.4.1. Definition of «age-related disease»:

3.4.1.1. Genetic predisposition;

3.4.1.2. The influence of environmental factors;

3.4.1.3. Lifestyle effect;

3.4.1.4. Race differences.

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

3.4.2.1. Atherosclerosis;

3.4.2.2. Arterial hypertension;

3.4.2.3. Insulin-independent diabetes type 2;

3.4.2.4. Intestine dysbacteriosis;

3.4.2.5. Autoimmune diseases;

3.4.2.6. Cancer;

3.4.2.7. Neurodegenerative process;

3.4.2.8. Osteoporosis.

3.4.3. Development of preventive measures for age-related diseases:

3.4.3.1. Drug-free methods;

3.4.3.2. Physical stress;

3.4.3.3. Diet;

3.4.3.4. Means of traditional medicine;

3.4.3.5. Pharmacological means.

3.4.4. The study of non-pathologic types of aging and phenomenon of longevity.

Section 4

IMMUNITY AND AGING

MAIN RESEARCH DIRECTIONS

In old age, diseases increase the immune deficiency which is typical for elderly people. It is quite possible to delay aging and abate manifestations of old age by preventing the weakening of normal immunity functions.

Main goals of aging study

- Detection of fundamental ways of age-related changes in the central and peripheral organs of immunogenesis.
- Development of new evaluation standards of genetic and immunological status influencing the aging rate.
- The study of the character of immune response toward various antigens of narrow specificity of inbred and congenic mice lines to understand the interrelations between the strength of genetic immunity force lifespan.
- Determination of the influential mechanisms of endogenous (autoimmune diseases, cells mutations) and external causes to immune system and the adding rate (chemical, industrial pollutants, uncontrollable pharmacological drugs, hypodynamia, psycho-emotional stress, the influence of electromagnetic radiation).
- Creation of methods for the immune correction of age-related changes and slowing of the aging process.
- Determination of mechanisms preventing mutational stream in the course of individual development. Radical longevity increase is impossible without understanding immunological control mechanisms.

4.1. FUNDAMENTAL INVESTIGATIONS OF THE IMMUNE SYSTEM DURING AGING

- 4.1.1. Investigation of interaction between aging and function of the immune system organs.
 - 4.1.1.1. Investigation of age-related changes in the central and peripheral immunogenic organs:
 - 4.1.1.1.1. Investigation of age-related changes in the central immunogenic organs:
 - 4.1.1.1.1.1. Investigation of the mechanisms of age-related thymus involution,
 - 4.1.1.1.1.2. Investigation of the role of peptide bioregulators of the «cytomedine» class generated by hypophysis and epiphysis in controlling the thymus activity
 - 4.1.1.1.1.3. Investigation of bone marrow as the primary organ of the immune system including the reasons for decrease in the number of stem cells and disorder of their differentiation.
 - 4.1.1.1.2. Investigation of age-related changes in the peripheral or secondary immunogenic organs:
 - 4.1.1.1.2.1. lymph nodes;
 - 4.1.1.1.2.2. spleen;
 - 4.1.1.1.2.3. the system of lymphoepithelial masses in mucous tunic of different organs.
 - 4.1.1.1.3. Investigation of interconnection between the central and peripheral organs of immunogenesis in the course of aging.
 - 4.1.1.1.4. investigation of age-related changes in immune privileged organs and tissues:
 - 4.1.1.1.4.1. CNS,
 - 4.1.1.1.4.2. testicles,
 - 4.1.1.1.4.3. eyes,
 - 4.1.1.1.4.4. thymus parenchyma.
- 4.1.2. Investigation of cell immunity as the main factor of body protection against viruses, pathogenic fungi, intracellular bacteria, tumors.



- 4.1.2.1. Study of innate immunity:
- 4.1.2.1.1. granulocytes;
 - 4.1.2.1.2. natural killers (NK, NKT).
- 4.1.2.2. Study of adaptive immunity:
- 4.1.2.2.1. cytotoxic T-lymphocytes:
 - 4.1.2.2.1.1. α -interferon;
 - 4.1.2.2.1.2. β -interferon;
 - 4.1.2.2.1.3. γ -interferon.
 - 4.1.2.2.2. T-helpers (Th):
 - 4.1.2.2.2.1. Th1 – cytokine production:
 - 4.1.2.2.2.1.1. γ -interferon;
 - 4.1.2.2.2.1.2. interleukin-2.
 - 4.1.2.2.2.2. Th2 – cytokine production:
 - 4.1.2.2.2.2.1. interleukin-4;
 - 4.1.2.2.2.2.2. interleukin-5;
 - 4.1.2.2.2.2.3. interleukin-10;
 - 4.1.2.2.2.2.4. interleukin-1;
 - 4.1.2.2.2.2.5. TGF- β .
 - 4.1.2.2.3. T-suppressors (CD4+CD25+Foxp3+T-regulatory cells):
 - 4.1.2.2.3.1. macrophages;
 - 4.1.2.2.3.2. dendritic cells.
- 4.1.2.3. Study of morphofunctional and phenotypic features of immunity effectors during aging:
- 4.1.2.3.1. Change in the quantity and correlation of immunocompetent cells:
 - 4.1.2.3.2. Correlation of mononuclear and polymorphonuclear leukocytes;
 - 4.1.2.3.3. Neutrophil generation and function:
 - 4.1.2.3.3.1. chemotaxis and chemokines production;
 - 4.1.2.3.3.2. intensity of "oxygen explosion" processes;
 - 4.1.2.3.3.3. phagocytic activity;
 - 4.1.2.3.3.4. expression conglutination molecules and TREM- (triggering receptor expressed on myeloid cell-1);
 - 4.1.2.3.3.5. bactericidal ability.
 - 4.1.2.3.4. Lymphocyte functional disorder:
 - 4.1.2.3.4.1. Th1/Th2 lymphocytes disbalance;
 - 4.1.2.3.4.2. spontaneous and induced generation of pro- and anti-inflammatory cytokines;
 - 4.1.2.3.4.3. NK activity;
 - 4.1.2.3.4.4. proliferative activity.
 - 4.1.2.3.5. Changed functional activity of phagocytes:
 - 4.1.2.3.5.1. phagocytic activity of neutrophils and macrophages;
 - 4.1.2.3.5.2. dendritic cell generation and aging processes;
 - 4.1.2.3.5.3. antigen-presenting capacity of macrophages and dendritic cells (DC);
 - 4.1.2.3.5.4. cytokines production by dendritic cells.
 - 4.1.2.3.6. Immunophenotype disorders:
 - 4.1.2.3.6.1. Lymphocytes:
 - 4.1.2.3.6.1.1. T / B cell ratio;
 - 4.1.2.3.6.1.2. CB4+/CB8+ cell ratio;
 - 4.1.2.3.6.1.3. NK and NKT cells content;
 - 4.1.2.3.6.1.4. T-regulatory cells (suppressors) (CD4+CD25+Foxp3+);
 - 4.1.2.3.6.1.5. T-helper clone formation;
 - 4.1.2.3.6.1.6. decreased ability of the body to recognize antigens;
 - 4.1.2.3.6.1.7. blast-transformation and killer potential of activated lymphocytes.
 - 4.1.2.3.6.2. macrophage and dendritic cells:
 - 4.1.2.3.6.2.1. expression of molecules of antigenic presentation and co-stimulating molecules;
 - 4.1.2.3.6.2.2. expression of pattern-recognizing receptors;
 - 4.1.2.3.6.2.3. expression on dendritic cells markers of terminal differentiation.
 - 4.1.2.3.6.3. cytokine production:
 - 4.1.2.3.6.3.1. Th1 /Th2 cytokine balance;
 - 4.1.2.3.6.3.2. spontaneous and induced production of cytokines by mononuclear leukocytes;
 - 4.1.2.3.6.3.3. spectrum of cytokines produced by macrophages and dendritic cells;
 - 4.1.2.3.6.3.4. cytokines genes expression;
 - 4.1.2.3.6.3.5. allelic polymorphism of cytokine genes and cytokine receptor genes: role in the

aging process.

- 4.1.2.3.6.4. Study of Th1/ Th2 cells balance.
- 4.1.2.3.6.5. Treg influence by antigen-presenting cells on expression of co-stimulating molecules.
- 4.1.2.3.6.6. Evaluation of intercellular cooperation disorders.
- 4.1.2.3.6.7. Investigation of morphological specificity of lymphocytes and antigen-presenting cells during aging.

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

- 4.1.3.1. Investigation of the functioning mechanisms of antibodies of different classes and subclasses during aging:
 - 4.1.3.1.1. antibody affinity;
 - 4.1.3.1.2. antigen neutralization;
 - 4.1.3.1.3. antigen opsonization;
 - 4.1.3.1.4. complement system activation.
- 4.1.3.2. Investigation of the possibility of restoring immune response as a trend in prophylaxis of age-related diseases.
- 4.1.3.3. Study of immunoglobulin disbalance mechanism in aging:
 - 4.1.3.3.1. age-related changes of IgM content at primary humoral response.
 - 4.1.3.3.2. IgG and IgA content at infectious process.
 - 4.1.3.3.3. Immunoglobulin disbalance - the reason for increased susceptibility of middle- and old-aged subjects to infections.
 - 4.1.3.3.4. Correlation of the content of memory B-cells and concentration of serum immunoglobulins.
 - 4.1.3.3.5. Antibody avidity.
 - 4.1.3.3.6. Mucosal immunity evaluation.
 - 4.1.3.3.7. Change of repertoire and variety of antibodies secreted by B-cells.

4.1.4. Investigation of genetic regulation of immunoreactivity in order to achieve longevity

- 4.1.4.1. Study of individual reactivity to common infectious antigens and allergens.
- 4.1.4.2. Study of human phenotype determining the functioning features of various organs and systems and possibly common behavioral reaction in the course of interaction with external environment.
- 4.1.4.3. Study of relation of histocompatibility complex and the sensitivity to viral infections, tumors and autoimmune diseases.
- 4.1.4.4. Investigation of the connection between the histocompatibility complex and pathological conditions (ankylosing spondylitis, reactive arthritis, acute anterior uveitis, juvenile diabetes, myasthenia gravis, celiac disease, dermatitis herpetiformis, Addison's disease, thyrotoxicosis, multiple sclerosis, complement C4 component deficiency etc.).
- 4.1.4.5. Investigation of the mechanisms of genetic control of immune response and its regulation in the process of aging.
- 4.1.4.6. Investigation of the role of histocompatibility complex genes in regulation of immunoreactivity and their connection with pathology.
- 4.1.4.7. Investigation of the connection between histocompatibility markers and lifespan.
- 4.1.4.8. Investigation of anti-inflammatory cytokine gene expression.

4.1.5. Immunological aging biomarkers

- 4.1.5.1. Identification of the immune risk phenotype:
 - 4.1.5.1.1. disorders of the phenotype and function of congenital and acquired immunity effectors;
 - 4.1.5.1.2. the specificity of cytokine profile;
 - 4.1.5.1.3. autoimmune reactions;
 - 4.1.5.1.4. development of a chronic inflammatory reaction;
 - 4.1.5.1.5. identification of the immuno-inflammatory status (inflamm-aging status) signs.

- 4.1.5.2. Search for typical immunity disorders during aging:
- 4.1.5.2.1. markers' expression and functional NK activity;
 - 4.1.5.2.2. phenotypical specificity of cytotoxic lymphocytes;
 - 4.1.5.2.3. antibody titer;
 - 4.1.5.2.4. establishment of the level of anti-inflammatory cytokines and pathogen-associated complexes in blood;
 - 4.1.5.2.5. assessment of translocation of bacteria and microbe-associated complexes (ligands of Toll-like receptors) from intestine.

4.2. INVESTIGATION OF INTERCONNECTION BETWEEN IMMUNITY DISORDERS AND ILLNESS RATE IN THE PROCESS OF AGING. DEVELOPMENT OF IMMUNOCORRECTION AND IMMUNOREHABILITATION METHODS

4.2.1. Investigations of the role of immune system in the process of aging

- 4.2.1.1. Influence on the nervous system
- 4.2.1.2. Influence on the condition of gastrointestinal tract
- 4.2.1.3. Influence on the cardiovascular system
- 4.2.1.4. Investigation of autoimmune reactions:
 - 4.2.1.4.1. autoantibodies, binding active enzymes, blood coagulation factors, and excess of hormones;
 - 4.2.1.4.2. persistent immunoinflammatory reaction – a triggering mechanism of development and/or progress of a number of diseases:
 - 4.2.1.4.2.1. atherosclerosis;
 - 4.2.1.4.2.2. Alzheimer's disease;
 - 4.2.1.4.2.3. osteoporosis;
 - 4.2.1.4.2.4. diabetes;
 - 4.2.1.4.2.5. myasthenia gravis;
 - 4.2.1.4.2.6. arthritis;
 - 4.2.1.4.2.7. sarcopenia (muscle mass reduction) and cachexy;
 - 4.2.1.4.2.8. infectious diseases.

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

- 4.2.2.1. Investigations of immunocorrection and immunorehabilitation of age-related changes in order to restore impaired immune homeostasis of the body:
 - 4.2.2.1.1. Immunostimulation – development of techniques of stimulating effect on various units of the immune system.
 - 4.2.2.1.2. Immunosuppression – development of techniques rendering suppressive action on this hyperfunctioning unit of the immune system or other.
 - 4.2.2.1.3. Immunomodulation – development of techniques to normalize immune functions depending on the initial condition of the immune system.
 - 4.2.2.1.4. Pharmacology – development of new geroprotectors reducing the risk of age-dependent diseases and facilitating cardinal life prolongation, and investigation of their action mechanism.
 - 4.2.2.1.5. Non-specific – action on all parts of the immune system as well as other organs and systems in order to facilitate immune system functioning.
 - 4.2.2.1.6. Specific – action on specific units of the immune system – targeted immunocorrection.
 - 4.2.2.1.7. Physiotherapy.
 - 4.2.2.1.8. Restoration of immune system disorders in sanatoriums and resorts.
- 4.2.2.2. Investigation of the influence of immunocorrection and immunorehabilitation in the process of aging on:
 - 4.2.2.2.1. Restoration of anti-infectious and anticancer immunity;
 - 4.2.2.2.2. Reduction of the risk of autoimmune diseases;
 - 4.2.2.2.3. Smoothing of manifestations of a chronic immuno-inflammatory reaction (inflamm-aging status).

4.3. INTRATHYMIC SELECTION AND AGING: DEVELOPMENT OF TRANSGENIC MODELS AND IMMUNE SYSTEM CORRECTION METHODS

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

4.3.1.1. Obtaining transgenic animals expressing alpha- and beta-chains of autoreactive T-cell receptor (TCR), specific to MNS of class II antigens.

4.3.2. Investigation of the conditions for selection of autoreactive T-cells in thymus of transgenic animals

4.3.3. Investigation of autoimmune pathological processes in transgenic animals carrying autoreactive T-lymphocytes

4.3.3.1. Investigation of changes in the behavior, memory, skin and hair, development of intestinal diseases, inflammatory reactions etc.)

4.3.3.2. Investigation of the pathomorphology of pathological processes, dynamics and development mechanisms.

4.3.4. Investigation of interconnection between selection of autoreactive T-lymphocytes and age-related thymus involution.

4.3.5. Development of the methods of affecting the process of intrathymus selection of autoreactive T-cells in transgenic animals.

4.3.5.1. Tree-structured tetramer peptides with the contact site sequence of MNS antigen molecules with T-cell receptors – as a promising tool of controlling selection of autoreactive T-lymphocytes in the thymus. Tetramer synthesis, optimization of their structure in order to achieve best biological effect, elaboration of the regimen of administration to transgenic animals.

4.3.5.2. Evaluation of the possibility of autoimmune disease prevention and treatment in transgenic animals by

administration of tree-structured peptides.

4.3.5.3. Identification of the influence of tetramer peptides on lifespan and occurrence of tumors in transgenic animals and wild-type animals.

Section 5

STEM CELLS AND AGING

MAIN RESEARCH DIRECTIONS

Since stem cells are a part of any organism and come into life and die together with the organism, it seems appropriate to take a closer look at the following points, first of all:

1. The “Aging” of stem cells and their specific niches as a loss of regenerative potential of the organism and manifestation of the aging phenotype.
2. Preservation of “young” stem cells.
3. Tumor stem cells.
4. The stem cells’ potential to restore organ functioning and tissue which had been lost due to aging.
5. The study of molecular and genetic qualities of ever-young, immortal, niche-independent human stem cells with the purpose of finding targets and models for “immortal” substance screening.
6. Genetically induced pluripotent stem cells.

5.1. STUDY OF STEM CELLS AND THEIR SPECIFIC NICHES “AGING” AS A PROCCESS OF LOSS OF THE ORGANISM’S REGENERATION POTENTIAL AND MANIFESTATION OF THE AGING PHENOTYPE

5.1.1. Study of genetic features of regional stem cells in the process of aging of the organism.

5.1.1.1. Search and study of the genes defining stem cells’ regenerative potential, including:

5.1.1.1.1 genes regulating pRB/p53 cellular cycle,

5.1.1.1.2. genes defining structure of cytoskeleton, structure of cytoskeleton, e.g. A-lamin,

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

5.1.1.1.4. MAP kinases,

5.1.1.1.5. oxidative stress genes.

5.1.2. Detection of factors which contribute to DNA integrity preservation and search for the ways to restore abilities of an aging stem cell to repair.

5.1.2.1. Study of changes which occur in the system of stem cells’ DNA integrity repair of an adult organism (deterioration of double-stranded break repair, coupling of nonhomologous ends of DNA, single-stranded break repair etc.)

5.1.2.2. Study of already discovered enzymes (e.g., Lig4) which need an activation to ensure better stem cells’ DNA repair in the process of aging.

5.1.2.3. Detection of other enzymes, which are losing activity over the time.

5.1.3. Study of epigenetic changes of stem cells’ during aging (methylation of DNA, deacetylation and methylation of histons, irreversible changes of chromatin et al.)

5.1.4. Study of the 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.

5.1.4.1. Study of the effect of stromal cells of the marrow tissue on aging of haematogenic stem cells.

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

5.1.4.3. Study of the ability of the niche cells to support stem cells' regeneration potential through secretion of growth-stimulating factors (e.g. BMPs (bone morphogenic proteins), which are released by niche cells, support germinal stem cells proliferation)

5.1.4.4. Study of the 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.

5.1.4.5. Development of methods of impacting niche cells to increase regeneration potential of stem cells, which do not interfere with internal signaling pathways of the stem cells, aimed at reduction of their tumorigenicity.

5.2. DEVELOPMENT OF METHODS AND TECHNIQUES FOR PRESERVATION OF REGIONAL STEM CELLS OF A YOUNG ORGANISM FOR THEIR POSSIBLE FUTURE APPLICATION

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

5.2.1.1. haematogenic stem cells from umbilical blood;

5.2.1.2. stromal stem cells from placental complex;

5.2.1.3. dental pulp stem cells;

5.2.1.4. hair follicle stem cells;

5.2.1.5. endometrium mesenchymal cells;

5.2.1.6. other types of stem cells, which require more invasive procedures.

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

5.2.3. Development of methods of cryopreservation and defrosting of the sample material.

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

5.3. STUDY OF TUMOR STEM CELLS AND DEVELOPMENT OF METHODS OF INFLUENCE ON THEM WITH THE PURPOSE OF STRUGGLE AGAINST ONCOLOGICAL DISEASES

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

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

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

5.4. STUDY OF STEM CELLS SUITABILITY TO RESTORE ORGAN OR TISSUE FUNCTIONS WHICH WERE LOST DUE TO AGING

5.4.1. Study of stem cells capabilities for the treatment of age-related diseases associated with attenuation of myocardium function and tissue blood supply.

5.4.1.1. Finding myocardium stem cells, detection and study of ways of their reactivation.

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

5.4.1.3. Carrying out 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.)

5.4.2. Study of possible use of stem cells for the treatment of age-related neurodegenerative diseases.

5.4.2.1. 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 neurones) or their loss (Alzheimer's disease) accompanied by prionation of proteins.

5.4.3. Study of stem cells application for the treatment of age-associated diseases related to deterioration of musculoskeletal system.

5.4.3.1. Carrying out a clinic research of bone tissue and articular cartilage regeneration using autologous mesenchymal multipotent stromal marrow cells which are able to differentiate into precursors of bone and cartilage tissue.

5.4.3.2. Carrying out the research aimed to obtain cells from fat tissue, which are similar in their potential to autologous mesenchymal multipotent stromal marrow cells.

5.5. STUDY OF MOLECULAR MECHANISMS OF IMMORTAL HUMAN STEM CELLS, NON-DEPENDENT OF A NICHE, FOR DETECTION OF TARGETS AND MODELS OF ANTI-AGING

5.5.1. Detection of protein and genetic factors of mESC (mouse embryonic stem cells) and hESC (human embryonic stem cells) which allow immortality to dominate over aging program:

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

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

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

5.5.1.4. In epigenetic state of ESC genome.

5.5.2. 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.

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

5.5.3.1. Study of a possible use of differentiated hESC to restore integrity of a nerve tract (oligodendrocytes secreting basic myelin protein, disseminated sclerosis, trauma).

5.5.3.2. Study of a possibility to obtain dopaminergic neurons for transplantations in case of parkinsonism.

5.5.3.3. Study of a possible use of vascular endothelium cells or their precursors for the treatment of pathologies associated with the vasculature including age-related pathologies.

5.5.3.4. Developing of protocols of hESC differentiation into stem or differentiated blood cells.

5.5.3.5. Establishment of characterized hESC lines cell bank, a standardized and inexhaustible source for blood-producing cells.

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

5.5.3.7. Study of a possibility to differentiate hESC into insulin-producing cells.

5.5.3.8. Study of hESC differentiation to cardiomyocytes and development of modes of transmission (imposition, electro-mechanic programming) of the pacemaker activity of an adult organism to the cells obtained in vitro

for coupling during transplantations (also some other rhythms, including circadian).

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

- 5.5.4.1. Development of techniques of selecting differentiated derivatives to reduce non-differentiated ESC proliferation potential.
- 5.5.4.2. Establishment of 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).
- 5.5.4.3. Study of a possible adaptation of the parthenogenesis method, which was developed for primates, to humans.
- 5.5.4.4. Study of a 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).

5.6. STUDY OF iPS CELLS OR CELLS WITH INDUCED PLURIPOTENCY (CELLS WHICH BEING INFLUENCED BY CERTAIN EXOGENOUS FACTORS CAN BE BROUGHT TO ESC-LIKE CELLS)

- 5.6.1. Study of a possibility to genetically re-program recipient's somatic cells.
- 5.6.2. Development of highly effective techniques which allow to change cells' status using transcription factors without employment of viruses, without genome integrity derangement, without oncogenes expression increase.
- 5.6.3. Study of the immortality level of the genetically induced pluripotent stem cells in culture in vitro.

Section 6

APPLICATION OF STEM CELLS IN GERIATRICS & GERONTOLOGY

MAIN RESEARCH DIRECTIONS

Stem cell therapy could be based on two major approaches, namely cell replacement and regeneration.

Regenerative cell therapy presumes stimulation of the body own cells, including that with proliferative activity (stem cells and progenitor cells). At the same time, cell replacement therapy relies upon a transplantation of various cell types, including highly differentiated functional cells, stem cells and progenitor cells.

By the moment, a large number of stem cells (SCs) and cells possessing some of their features is known. A biological variety of SCs is impressive; it thus defines an ability to apply some types of the latter for particular clinical causes. From the practical point of view, cell therapy could aim preventing a development of particular pathology, or target a pathology already developed.

Active studies of basic mechanisms underlying unique features of SCs are currently underway. Further development of these studies would play a major role in developing protocols of SC- or SC derivatives application as cell replacement therapy substrate. It would also contribute to the protocols aiming regulation of body own stem and progenitor cells functions.

It should be particularly stressed that adaptation of techniques well-tested in the laboratory to the requirements of clinical practice requires utilizing a joint multidisciplinary approach. Actually, any SC-based protocol requires utilization of modern genetics/genomics and proteomics methods, making new materials (e.g., cell culture medias and surfaces) and hardware (e.g., bioreactors for effective SC expansion).

Therefore, only joint efforts of specialists in different disciplines within a mainframe of the Program could ensure an effective application of cell technologies both in experimental biology and in practical medicine. Clinical geriatrics represents the field of choice in the latter.

Stem cell application in gerontology:

1. SCs as a research target;
2. SCs and SC derivatives as models of therapeutic targets;
3. SCs and SC derivatives as cell replacement therapy substrates;
4. SCs as a mean of drug substance address delivery;
5. SCs as a mean of imaging (diagnostic) substance address delivery.

6.1. STUDIES OF BASIC MECHANISMS OF STEM CELL BIOLOGY

6.1.1. Acquiring SCs as a study subject;

- 6.1.1.1. Defining a logistics of acquiring SC subtypes (based on a system of state control);
- 6.1.1.2. Refinement of highly effective protocols for SC subtype acquiring;
- 6.1.1.3. Acquiring SC of the types suitable for long-term culturing in vitro, and characterization of these;
- 6.1.1.4. Control of SC lines features, including:
 - 6.1.1.4.1. genome stability,
 - 6.1.1.4.2. lack of transformation,
 - 6.1.1.4.3. perpetuation of pluripotency past numerous passages in vitro;
- 6.1.1.5. Refinement of highly effective protocols for SC subtype cultured in vitro (including feeder cell subtypes-based);
- 6.1.1.6. If necessary, development of novel culture media preparations and identification of growth factors essential for effective SC subtypes cultivation in vitro;
- 6.1.1.7. Expansion of SC subtype lines;
- 6.1.1.8. Refinement of highly effective protocols for in vitro cultured SC subtypes banking and shipping (cryotechniques-based);

6.1.2. Studies of basic mechanisms of SC growth, differentiation and aging;

- 6.1.2.1. Identification of the factors affecting proliferation features of both in vitro cultured SC subtypes and SCs in vivo, using high-throughput means of modern genomics, proteomics and metabolomics;
- 6.1.2.2. Studies of mechanisms underlying a loss of proliferation activities by in vitro cultured SC subtypes (as a consequence of SC and feeder cell replicative aging, malignant transformation, etc.);
- 6.1.2.3. Identification of the factors (including physical, chemical and biological) initiating and directing SC subtype differentiation. In particular, includes the following:

6.1.2.3.1. Identification of the genes initiating a program of SC subtypes differentiation in response to:

- 6.1.2.3.1.1. unspecific factors,
 - 6.1.2.3.1.2. specific factors,
 - 6.1.2.3.1.3. identification of the means for repression or stimulation of these genes (via genetic engineering);
- 6.1.2.3.2. Following SC derivatives by using marker protein-encoding genetic constructs (via genetic engineering);
- 6.1.2.3.3. Identification of unspecific factors (or combinations of factors) participating in control for SC subtype differentiation. In particular, includes the following:
- 6.1.2.3.3.1. Special cell surfaces for culturing SCs in vitro (Matrigel, collagen I, polyornitine, laminine/fibronectin, etc.);
 - 6.1.2.3.3.2. Special cell culturing regimens (hypoxia, mechanical stimulation of the cells);
 - 6.1.2.3.3.3. Co-culture systems (culturing SCs with other cell types, like PA6 and OS5);
 - 6.1.2.3.3.4. Cell culture media conditioning (over other cell line cultures) and their application for promoting and refining SC in vitro differentiation protocols;

6.1.3. Application of SCs as biological markers of physiological parameters and diseases;

- 6.1.3.1. Identification of genetic (qualitative and quantitative) makers for SC subtype populations in vivo;
- 6.1.3.2. Identification of the protein markers for SC subtype populations in vivo;
- 6.1.3.3. Refinement of the protocols for SC identification in biological specimen and tissues;
- 6.1.3.4. Interpretation of the results achieved (merging qualitative and quantitative information with physiological status and prognosis).

6.2. STEM CELL-BASED CELL REPLACEMENT THERAPY APPLICATIONS

6.2.1. Development of approaches based on the affecting body own stem and progenitor cells:

- 6.2.1.1. Development of approaches based on the stimulation of the body own stem and progenitor cells by the therapeutic factors;
- 6.2.1.2. Development of approaches based on the repression of the body own stem and progenitor cells by the therapeutic factors.

6.2.2. Establishment of safety means associated with application of SCs and SC derivatives as the substrates of cell replacement therapy:

- 6.2.2.1. Infectious disease-associated complications, including:
 - 6.2.2.1.1. Viral infections;
 - 6.2.2.1.2. Bacterial infections;
 - 6.2.2.1.3. Parasitic infections;
 - 6.2.2.1.4. Fungal infections (mycoses);
 - 6.2.2.1.5. Prion diseases;
- 6.2.2.2. Hereditary disease-associated complications, including:
 - 6.2.2.2.1. Metabolic disorders;
 - 6.2.2.2.2. Hemoglobinopathies;
- 6.2.2.3. Acquired disease-associated complications, including:
 - 6.2.2.3.1. Autoimmune diseases;
 - 6.2.2.3.2. Oncological diseases (including hemoblastoses leukoses), benign tumors formed in the transplantation site (due to the uncontrollable proliferation of transplanted stem cells and progenitor cells), including teratoma;
 - 6.2.2.3.3. Other nonhematological oncological diseases developed due to the contamination of donor material with tumor cells (including metastatic cells);
- 6.2.2.4. Xenozoonoses, including:
 - 6.2.2.4.1. Viral diseases;

6.2.2.4.2. Diseases caused by a contamination of cell material with animal cells, including SC purification, expansion and in vitro differentiation steps;

6.2.2.4.3. Diseases caused by animal products utilization throughout the SC (including human SC) works: SC purification, expansion, etc.

6.3. STEM CELL-BASED CELL APPLICATIONS UNRELATED TO CELL REPLACEMENT THERAPY

6.3.1. Application of SCs and their derivatives as therapeutic models:

- 6.3.1.1. Effective expansion of SC subtypes;
- 6.3.1.2. Effective in vitro differentiation of SC subtypes to the cells of various organs and tissues;
- 6.3.1.3. Testing cells with candidate substances (drug candidates and biologically active preparations) in various regimens.

6.3.2. Development of approaches based on using SCs as the means of address delivery for drugs and biologically active preparations;

- 6.3.2.1. Effective expansion of SC subtype lines;
- 6.3.2.2. If necessary, effective in vitro differentiation of SC subtypes to the cells attracted to the particular tissues;
- 6.3.2.3. Modification of SC and their derivatives to be applied as temporary carriers of drugs and biologically active preparations, released in the target tissues in a specific manner;

6.3.3. Development of approaches based on using SCs as the means of address delivery for imaging substances (visualized at diagnostic procedures):

- 6.3.3.1. Effective expansion of SC subtype lines;
- 6.3.3.2. If necessary, effective in vitro differentiation of SC subtypes to the cells attracted to the particular tissues;

6.3.3.3. Modification of SCs and their derivatives to be applied as temporary carriers of imaging substances, released in the target tissues in a specific manner;

6.3.3.4. Development of technologies (or adaptation of the existing ones) for diagnostic substances microvolume visualization in tissues and organs;

6.3.4. Development of approaches based on using SCs as the means of genetic material address delivery (in a form of gene therapy or gene/cell therapy):

6.3.4.1. Effective expansion of SC subtype lines;

6.3.4.2. If necessary, effective in vitro differentiation of SC subtypes to the cells attracted to the particular tissues, with a defined set of features (presence of lack of proliferation potential, functional activity, etc.);

6.3.4.3. Identification of genes able to affect physiological processes in the target tissues and organs;

6.3.4.4. Genetic modification of the cells (by genetic engineering means) and confirmation of defined cell feature set persistence past that;

6.3.4.5. If necessary, development of cells system with a modified set of features, such as:

6.3.4.5.1. insertion of genes coding marker proteins (e.g., fluorescent) to the cellular genome;

6.3.4.5.2. utilization of the inducible genetic construct to be activated or shot-down by the defined antibiotic;

6.3.4.6. Experimental confirmation of the specificity of address delivery of genetic material to the tissues by SCs and their derivatives, and of a safety of the procedure.

6.3.4.7. Enforcement of follow-up control in regards to potential malignant transformation of genetically modified cells;

6.3.4.8. Establishment of a system of state control for research studies in the field of gene therapy.

6.3.5. Studies of SCs as a source of biologically active substances:

6.3.5.1. Studies in the field of direct derivation of biologically active substances (e.g., growth/transcription factors) off culture media conditioned over the cultures of SCs or SC derivatives;

6.3.5.2. Applications of genetically modified SCs or SC derivatives for the biosynthesis of precious biologically active substances (as "bioreactors", similar to that applied in human insulin and growth/transcription factors synthesis by the competent cells);

6.3.5.3. Development of technology for industrial-scale manufacturing and purification of biologically active substances using SCs and/or SC derivatives.

6.4. STEM AND PROGENITOR CELL-BASED APPLICATIONS IN CLINICAL GERIATRY

6.4.1. Development of comprehensive criteria system for cell therapy applicability in particular clinical cases, with precise methodology and control.

6.4.2. Adaptation of existing antiepidemic means (to prevent infectious complications development in cell therapy recipients) to cell replacement therapy practices, with precise methodology and control at every step.

6.4.3. Adaptation of existing SC collection and expansion techniques to cell replacement therapy practices:

6.4.3.1. Refinement of highly effective protocols for SC subtypes collection with no xenogenic product exposure, including the following:

6.4.3.1.1. Fetal bovine serum/fetal calf serum;

6.4.3.1.2. Serum replacement;

6.4.3.1.3. Enzymes of animal origin;

6.4.3.2. Refinement of highly effective protocols for SC subtypes expansion with no xenogenic product exposure, including the following:

- 6.4.3.2.1 Fetal bovine serum/fetal calf serum;
- 6.4.3.2.2. Serum replacement;
- 6.4.3.2.3. Enzymes of animal origin;
- 6.4.3.2.4. Surface covers of animal origin (gelatine, laminine, collagene, fibronectin, Matrigel, etc.);
- 6.4.3.2.5. Growth factors of animal origin (e.g., fibroblast growth factor 2 (FGF-2, bFGF).
- 6.4.3.3. Adaptation of the protocols aiming large-scale expansion of SC subtypes, with reduced length and associated expenses of those protocols (using automated SC culture systems and "bioreactors", when possible).
- 6.4.4. Foundation of effective clinically oriented "Stem cell banks" on different levels (national, regional, institutional).
- 6.4.5. Adaptation of existing SC and SC derivatives long-term storage and shipping techniques to cell replacement therapy practices:
 - 6.4.5.1. Refinement of cell shipping technology,
 - 6.4.5.2. Refinement of cell shipping logistics,
 - 6.4.5.3. Foundation of an appropriate state control system;
- 6.4.6. Adaptation of existing techniques of SC subtypes in vitro differentiation to functional cells suitable for transplantation to cell replacement therapy practices:
 - 6.4.6.1. Modification of highly effective protocols of SC subtypes in vitro differentiation to functional cells (refined for the laboratory practices) in regards to complete elimination of animal cells and materials of animal origin;
 - 6.4.6.2. Adaptation of existing protocols aiming scaling up SC subtypes in vitro differentiation to functional cells, with reduced length and associated expenses of those protocols (using automated SC culture systems and "bioreactors", when possible);
 - 6.4.6.3. Establishment of the strict control over the proliferation of SC subtypes derivatives, with adaptation of the techniques developed to the abilities of the clinical centers.
- 6.4.7. Refinement of cell (SC subtypes and their derivatives) transplantation techniques in a form of cell replacement therapy:
 - 6.4.7.1. Refinement of cell material processing for transplantation procedure:
 - 6.4.7.1.1. Establishment of control measures in regards to contamination of cell substrates with infectious agents and residual cells with high proliferative activity;
 - 6.4.7.1.2. Refinement of cell (SC subtypes and their derivatives) processing for transplantation procedure (e.g., monolayer to cell suspension);
 - 6.4.7.2. Refinement of cell injection technique for maximal clinical effect (local or system delivery, via stereotaxic surgery, etc.);
 - 6.4.7.3. Refinement of techniques improving SC and SC derivatives survival, including:
 - 6.4.7.3.1. Application of gentle methods for cell dissociation;
 - 6.4.7.3.2. Shortening of cell processing and injection protocols;
 - 6.4.7.3.3. Application of unspecific and specific factors improving cell survival, when injected together with cells;
 - 6.4.7.4. Refinement of surgery technique allowing transplantation of cells precisely to the selected anatomical structure.
- 6.4.8. Adaptation of a technique based on the effective and safe genetic modification of SC subtypes and their derivatives, to the clinical needs (to be applied as gene therapy or gene/cell therapy):
 - 6.4.8.1. Adaptation of a logistics of genetically modified SC and SC derivatives to the clinical needs, with recommendations on the following subjects: delivery, registration, control, safety issues;

- 6.4.8.2. Establishment of the specific set of criteria for gene or gene/cellular therapy application in the particular clinical cases;
 - 6.4.8.3. Enforcing clinical trials allowing generating a reliable data on the effectiveness of SC and SC derivatives application in the form gene or gene/cell therapy in the particular clinical cases;
 - 6.4.8.4. Enforcing long-term follow-up control in regards to potential malignant transformation of genetically modified cells;
 - 6.4.8.5. Development of a system of state control for clinical application of gene therapy.
- 6.4.9. Adaptations of the approaches based on the stimulation of the body own stem and progenitor cells to the clinical requirements, in the format of regenerative cell therapy:**
- 6.4.9.1. Enforcing clinical trials allowing generating a reliable data on the effectiveness of selected therapeutic approaches in the particular clinical cases;
 - 6.4.9.2. State registration of the techniques based on the stimulation or inhibition of body own stem and progenitor cells in the particular clinical cases;
 - 6.4.9.3. Wide application of the techniques developed to the clinical practice, for specific causes.
- 6.4.10. In particular cases, development of the approaches based on SC and SC derivatives application in "tissue engineering". Clinical tests of the materials acquired:**
- 6.4.10.1. Development of biologically compatible (and biodegradable) materials suitable for SC derivatives culturing, differentiation and/or functioning. Technological bases for this task could, for example, be based on the nanotechnologies;
 - 6.4.10.2. Refinement of the protocols for "seeding" of the base (2D or 3D) with cells, followed by the culturing and/or final differentiation of SC derivatives;
 - 6.4.10.3. Refinement of surgery technique
- utilizing "artificial tissue" (e.g., bone tissue), for specific causes;
 - 6.4.10.4. Enforcing clinical trials allowing generating a reliable data on the effectiveness of "tissue engineering"-based approaches in the particular clinical cases;
- 6.4.11. Development of most comprehensive criteria for cell therapy applications in the particular clinical cases;**
- 6.4.12. Refinement of effective and safe regimens for immunosuppression therapy, as applied with SC subtypes and their derivatives in the clinical practice:**
- 6.4.12.1. Wide application of modern techniques allowing evaluation of immunosuppression therapy adequacy (e.g., by measuring substance concentration in the biological specimen);
 - 6.4.12.2. Development of the schemes for immunosuppression therapy adapted for cell replacement therapy requirements, with variations for SC subtypes and their derivatives, various injection sites, various immune status of recipients, etc.
- 6.4.13. Refinement of a system of control means aiming minimizing or completely eliminating a risk of infectious, hereditary and oncological diseases caused by SC subtypes and their derivatives application in clinical practice:**
- 6.4.13.1. Establishment of criteria allowing preventing a development of hereditary disease in recipients (e.g., Gaucher disease, thalassemias); regulation of donor selection;
 - 6.4.13.2. Further refinement of antiepidemic means to prevent infectious complications development in cell therapy recipients, by strict regulation of work and enforcing control means on the following stages:
 - 6.4.13.2.1. donor selection;
 - 6.4.13.2.2. cell collection;
 - 6.4.13.2.3. cell processing (including

cell expansion, storage and shipping);

6.4.13.2.4. cell transplantation to recipients.

6.4.13.3. Development of technologies allowing a complete elimination of a risk of oncological complications caused by cell transplantation (primarily teratoma and non-teratoma tumors developed in the site of transplantation) by the following means:

6.4.13.3.1. refinement of a system of means granting a control over the proliferative status of SC subtypes derivatives;

6.4.13.3.2. utilization of unspecific factors of selection;

6.4.13.3.3. balancing the parameters of immunosuppression therapy.

6.4.13.4. Development of technologies allowing a complete elimination of a risk of malignant transformation of body own SCs (with their uncontrolled proliferation) as caused by the external factors.

6.4.14. Development of a system of means to control the effectiveness of cell therapy (by non-invasive diagnostic technologies and physiological/clinical criteria).

Section 7

MEDICATED GEROPROTECTION

MAIN RESEARCH DIRECTIONS

The main objective is to create a method for the selection of medication combinations (based on individual genetics, age, health status, lifestyle etc.), which would inhibit as much as possible (preferably – completely) the manifestation of physiologic aging.

7.1. GENERAL GEROPROTECTION RESEARCH ISSUES

- 7.1.1. Target setting in development of multi-criteria geroprotectors classification.
- 7.1.2. Develop methodological approaches and basis for geroprotectors' search and testing.
- 7.1.3. Establish correct pathomorphologic criteria of death cause definition in laboratory animals (e.g. primates).
- 7.1.4. Collation of pathophysiology of basic pathologic processes which lead to age-associated death in humans and laboratory animals in order to develop correct approaches to interpret the data on geroprotectors effects on longevity and death causes.
- 7.1.5. Create a scheme-listing of required integral indications and model systems for geroprotectors' screening.
- 7.1.6. Develop methods of drug combination selection that prove to be highly efficient in preventing age-related human pathologies. Develop mathematical methods of experiments planning and results analysis, including proper methods of small samplings processing.
- 7.1.7. Study if there is a physiologic necessity to keep aged cells in tissues.
- 7.1.8. Study of the possibility of modulation of cytokines secretion by aged cells.
- 7.1.9. Develop a drug that will inhibit synthesis of pro-tumor cytokines by aged cells or induce removal of such cells from tissues.
- 7.1.10. Analyze the possibility to activate DNA repair system as a geroprotection factor.
- 7.1.11. Analyze the possibility to activate inducible endogenous antioxidant systems (in particular, internal mitochondrial systems) as a geroprotection factor.
- 7.1.12. Research of the possibility to activate stress-factors, such as chaperones and heat-shock proteins as a geroprotection factor.
- 7.1.13. Research of the possibility of modulation of the sirtuin chain as a geroprotection factor.
- 7.1.14. Research of the effects of different geroprotectors on aging bio-markers.
- 7.1.15. Conduct an epidemiologic research of "aging markers" correlation to the rate of basic age-related diseases (diabetes, atherosclerosis, Alzheimer's disease etc.), accidents (myocardial infarction, cerebral accidents), incapacitation and death.
- 7.1.16. Research of the possibility to use chemical chaperones (glycerin and other polyatomic alcohols, trehalose and other sugars, some aminoacids, alkyloxybenzenes etc.) for protein stabilization and their fermentative activity inhibition.



7.2. RESEARCH OF GEROPROTECTIVE PROPERTIES OF MELATONIN

- 7.2.1. Continue research of melatonin's effect on cells transformation, oncogenes expression, apoptosis and senescence processes.
- 7.2.2. Study melatonin's regulative effect on mediators and peptides interchange in CNS.
- 7.2.3. Study melatonin's effect on hormones secretion (primarily by APUD-system).
- 7.2.4. Study melatonin's effect on telomerase expression and telomere length.
- 7.2.5. Study the impact on free radicals production in mitochondria and their afterlife in the cell.
- 7.2.6. Study extra-epiphysial melatonin's role in the organism.

7.3. RESEARCH OF GEROPROTECTIVE PROPERTIES OF PEPTIDES

- 7.3.1. Continuation of analysis of fractions peptide extracts of thymus and epiphysis extracted by different methods, research of their geroprotective activity.
- 7.3.2. Research of geroprotective properties of epithalon and epithalamin:
 - 7.3.2.1. Continue research of epithalon and epithalamin effect on genes expression mechanisms.
 - 7.3.2.2. Decrypt specific molecular mechanism of epithalon and epithalamin effect on target genes, determine mediators of these processes in order to synthesize more effective equivalent of these peptides.
 - 7.3.2.3. Study epiphysis peptides effect on the performance of APUD system (single hormone producing cells system) as

a possible target for epithalon and epithalamin drugs.

- 7.3.2.4. Study epithalon and epithalamin effects on adrenergic mediators metabolism in CNS and epiphysis sensitivity to noradrenergic stimulation.
- 7.3.3. Research of geroprotective properties of vilone, thymalin and thymogen.
 - 7.3.3.1. Continue research of effects of vilone, thymalin and thymogen on genes expression mechanism.
 - 7.3.3.2. Decipher specific molecular mechanism action of vilone, thymalin and thymogen on the target genes, establish mediators of these processes in order to synthesize more effective equivalents of these peptides.
- 7.3.4. Research of mechanism of action of deltaran:
 - 7.3.4.1. Study the effects of deltaran on oxidative processes in the body.
 - 7.3.4.2. Study the effect of deltaran on the various mechanisms of cancerogenesis, including oncogene expression, age-dependant accumulation of senescent cells and their ability to release pro-tumoral humoral factors.
- 7.3.5. Study the role of synthesis induction of antioxidative ferments and melatonin in geroprotective effects of peptide drugs of epyphysis.
- 7.3.6. Experimental and clinic research of known and newly synthesized peptide drugs on the model of human geriatric disease (diabetes, atherosclerosis, hypertonia and others) in laboratory animals.

7.4. RESEARCH OF GEROPROTECTIVE PROPERTIES OF GROWTH HORMONE

- 7.4.1. Find out possibility for increase on aging by effect on IGF-1 receptors.

- 7.4.2. Develop antagonist of IGF-1 receptors.

7.5 FULL RESEARCH OF GEROPROTECTIVE PROPERTIES OF THE FOLLOWING DRUGS, INCLUDING ANALYSIS OF PATHO-MORPHOLOGICAL CHANGES IN LABORATORY ANIMALS:

- 7.5.1. Thyroxin.
- 7.5.2. Cross-linking blocker (EDTA, β -aminopropionitrile, carnosine and L-acetylcarnosine, ALT711 (algebrum is a cross-linker destroyer)).
- 7.5.3. Adaptogens (extract of Redberry, Eleuterococcus, Ginkgo Biloba).
- 7.5.4. Fullerenes and their derivatives as antioxidants.
- 7.5.5. Vitamine E forms (tocopherols and tocotrienols).
- 7.5.6. Carotinoids (β -carotin, lycopene, lutein, astaxanthin, zeaxanthin et al.).
- 7.5.7. Succinic acid derivatives (Mexidol).
- 7.5.8. Flavonids, anthocyanins and others, polyphenols (Curcumin, Resveratrol, and relative compounds (Pterostilben), Quercetin and Dihydroquercetin, catechines and others).

7.6. RESEARCH OF GEROPROTECTIVE PROPERTIES OF NEUROTROPIC DRUGS

- 7.6.1. Finding out the scope of geriatric diseases and physiologic changes which are slowed down by deprenyl in order to conduct subsequent clinical research of this drug.
- 7.6.2. Establishing of a specific mechanism of action of Gerovital and its role in blocking of Mono-oxidase in aging deceleration. Examination of Gerovital's effect on longevity.

7.7. STUDY OF GEROPROTECTIVE PROPERTIES OF ANTIOXIDANTS

- 7.7.1. Study their effect on carcinogenesis caused by different agents; study their synergetic and antagonistic qualities to other drugs of this group and geroprotectors with a different mechanism of action.
- 7.7.2. Comparative research in vivo and in vitro of anti-oxidants' effects on the mechanisms of apoptosis and cellular aging.
- 7.7.3. Comparative research in vivo and in vitro of antioxidants' effects on cell differentiation process and production of cytokines by them.
- 7.7.4. Comparative research in vivo and in vitro of antioxidants' effects on the synthesis of autologous antioxidant ferments.
- 7.7.5. Comparative research in vivo and in vitro of antioxidants' effects on mitochondrial and nucleus DNA damage and certain key genes of anti-aging, telomeres and cell membrane structure.
- 7.7.6. Research antioxidants effect on endocrine control, especially on epiphysis and hypothalamo-pituitary axis capacity.
- 7.7.7. Research antioxidants effect on age-dependent characteristics of the immune system, in particular, on immunosenescence, naive T-lymphocytes count, self-reactive clones, thin changes in subpopulation structure of blood lymphocytes and immunocompetent organs.
- 7.7.8. Research of the antioxidants effects on models of different geriatric diseases – atherosclerosis, diabetes, retinopathy, osteoporosis and others and establish the scope of their clinical use (it relates to SkQ in the first place).
- 7.7.9. Comparative research of antioxidants' effects on genes expression, establishing gene

patterns which are most important in terms of their geroprotective effects manifestation.

- 7.7.10. Research of the possibility of stimulating body's proprietary antioxidant system.

7.8. RESEARCH OF BIGUANIDE GEROPROTECTIVE PROPERTIES

- 7.8.1. Decipher the true mechanism of of biguanides effect on aging processes and develop ways of approaching the elaboration of the most effective ones.
- 7.8.2. Establish the possibility of clinical use of biguanides as anti-aging drugs.

7.9. RESEARCH OF GEROPROTECTIVE PROPERTIES OF CALORIC RESTRICTION MIMETICS

- 7.9.1. Explore specific mechanism of geroprotective action of caloric restriction.
- 7.9.2. Verify the role of methionine in caloric restriction effects.
- 7.9.3. Research and study of caloric restriction mimetics.

7.10. DEVELOPMENT OF DRUGS TO IMPACT P66SHC SIGNALING

- 7.10.1. Synthesize signaling inhibitor p66shc which reproduces knock-out effects.
- 7.10.2. Conduct a research of geroprotective properties and side-effects of such an inhibitor.

7.11. SEARCH OF A SAFE ACTIVATOR OF TELOMERE ELONGATION

- 7.11.1. Research of effective activators of telomere elongation.

- 7.11.2. Research of the carcinogenic properties of the activators of telomerase expression.

- 7.11.3. Research of a method to elongate telomeres with no activation of telomerase expression (or with a subsequent inhibition of its expression).

- 7.11.4. Study of the telomere elongators' effect on longevity, physiologic indicators and pathomorphology of animals.

7.12. RESEARCH GUIDELINES IN GEROPROTECTION

- 7.12.1. Production of drugs aimed at lipofuscin accumulation slowdown.
- 7.12.2. Production of drugs aimed at lipofuscin degradation.
- 7.12.3. Research of a possibility to revitalize chromatin with the aid of drugs, e.g. histone deacylases.
- 7.12.4. Development of a fusion therapy of damaged spliceosomes.
- 7.12.5. Development of drugs and methods of protein inversion activation.
- 7.12.6. Drug development in order to increase chondriokinesis.
- 7.12.7. Development of a therapy to reinforce lysosomal enzymes.
- 7.12.8. Formulation of drugs and methods to increase expression of useful genes (e.g. Lamp2a, Lon, proteasome proteins, Klotho gene).
- 7.12.9. Research of specific features of peptides glycation and glucose assimilability. Design a drug to reduce glucose level.
- 7.12.10. Drug development to decelerate glycation.
- 7.12.11. Drug synthesis aimed at prevention of propagation of mutated mitochondria DNA clones.
- 7.12.12. Drug development on the basis of metal chelators to prevent

interaction between beta-amyloid and copper and zinc.

- 7.12.13. Drug development to destroy cross linking.
- 7.12.14. Drug development to stimulate fibroblast and MSC.
- 7.12.15. Drug design to selectively remove T-cells.
- 7.12.16. Development of methods of inhibition of immunosenescence and restoration of neuroendocrinal and immune systems.

Section 8

GEROPROTECTORS EFFICIENCY RESEARCH

MAIN RESEARCH DIRECTIONS

It is a very comprehensive task to carry out clinical trials and approve indications for lifespan-enhancing drugs. Given, that such drugs are to be taken by healthy people for a long period of time, sometimes for decades, mandatory top-rank safety requirements thereto seem to be quite reasonable.

It applies primarily to the side effects, the probability of which should be as close to zero as possible. If we witness a decrease in mortality over the course of the experiments, it will provide for longstanding, even decade-long, clinical trials.

All this adds to the constraints, as both patent legislation and regulatory requirements to these trials may be subject to modification during such a long period of time. An important factor here is the ethical demands towards performance and the issues of standardization of such trials.

We must admit to the absence of normative documents that can regulate the clinical trials of lifespan-enhancing drugs and, as of now, the US Food and Drug Administration does not approve such drugs.

Age-related detrimental effects inhibiting drugs can be introduced into preventive medicine through tests on people with specific age-related illnesses including various kinds of "accelerated aging" and states depending on whether the drugs offer resistance against the illness progression during short-term trials.

Based on research at the Gerontology Institute of the Academy of Medical Science of the Ukraine, people with signs of accelerated aging best fit geroprotector efficiency trials. According to O.V. Korkushko and coauthors (2003) this category can include patients with

ischemic heart disease. The authors consider ischemic heart disease as being a result of accelerated age-related modifications in the cardiovascular system and organism as such.

O.V. Korkushko et al.'s Monography (2003) contains a detailed description of the estimation procedure for the geroprotective impact of drugs in terms of thymus and epiphysis peptide medication. Drug efficiency has been estimated with the account of subjective state dynamics, the functional age of physiological body systems, physical and mental capacity, immunity, bone tissue, decontaminating liver function, lipidic blood spectrum, the tolerance to carbohydrates, tissue oxygen-exchange, vegetal regulation and blood-vessel gland functionality.

It should be noted that the research lasted for 6-12 years and the efficiency criterion for clinically tested thymus and epiphysis drugs was seen in a decrease in the patients' mortality if compared to a reference group of people who didn't receive geroprotectors.

8.1. DEVELOPMENT OF GUIDELINES FOR GEROPROTECTORS, EFFICIENCY RESEARCH IN TESTS ON LABORATORY ANIMALS AND CLINICAL TESTS ON PEOPLE

8.1.1. Experiment Model Selection

While planning a research the researcher has to answer three main questions:

1. Is the research cost reasonable in terms of the amount of animals required to obtain statistically credible results?
2. Are experimental conditions reproducible, including animals' genetics and characteristics?
3. Does the research model meet the objectives of the research?

8.1.2. Selection of Physiological Age Markers

Goals and objectives: determination of criterion for physiological age markers and development of a baseline markers list as well as an extended list thereof.

8.1.3. Development of unified test reports on potential geroprotectors efficiency in animals (monkeys, rats, mice, fruit flies, hookworms, yeast).

A test report should include the following animal data:

- type, line, sex,
- housing conditions,
- age at the beginning of the test,
- animal randomization principles,
- modes of drug administration,
- dosage and regimen of drug administration,
- peculiarities of animals monitoring,
- food and water consumption,
- somatic temperature,
- estrous function (females),
- animals motor performance (tests "open field", "shuttle maze" and "elevated plus maze"),
- physical strength and fatigability,
- required biochemical and hormonal tests, including telomere length,
- pathomorphological tests,
- life span characteristics,
- statistical methods of data processing.

8.2. DEVELOPMENT OF POTENTIAL GEROPROTECTOR LISTING FOR PRIME PRECLINICAL AND CLINICAL TRIALS

Is carried out by a group of researchers – gerontology and pharmacology specialists.

The listing can include:

1. Peptide epiphysis drugs (Epitalamin and Epitalon)
2. Melatonin
3. Metformin
4. SkQ-1
5. Deltaran
6. Resveratrol
7. Rapamicin
8. Succinic acid
9. Glycation inhibiting drugs
10. Deprenil
11. Entero sorbents
12. Development of efficient geroprotector combinations

8.3. DEVELOPMENT OF POTENTIAL GEROPROTECTOR EFFICIENCY ASSESSMENT PROGRAM

The program is targeted at development of a critical review, system and methods for geroprotective activity and efficiency assessment of a drug or another preparation. Experts could also provide advising on the credibility of additional researches.

Criteria for assessment can be defined as a proved efficiency degree of certain recommendations for geroprotectors use.

There are four degrees:

1. There is sufficient proof of the drug geroprotector efficiency confirmed by epidemiological multicenter randomized researches;
2. Drug efficiency has been confirmed by numerous experimental tests on various animals, while there is no sufficient efficiency proof obtained in epidemiological multicenter randomized researches or such proof has been the result of individual monitorings;
3. There are sporadic reports on drug efficiency with high-level reliability;
4. There are sporadic unconfirmed reports on drug efficiency.

8.4. DEVELOPMENT OF A GEROPROTECTOR CLINICAL TRIALS REPORT

8.5. DEVELOPMENT OF A MATERIAL AND TECHNICAL BASE “GEROPROTECTORS” (FOR EXAMPLE)

Setup of a Scientific and Production Center “Geroprotector”, including:

1. SPF vivarium (20,000-30,000 rodents)
 - Outbred mice
 - Inbred mice
 - Transgenic and genetically modified mice
 - Rats
 - Fruit flies
 - Hookworms
 - Yeast
2. Veterinary and Genetic Control Laboratory
3. Scientific-Research Division
Laboratories of:
 - molecular biology
 - cytoogerontology
 - pathomorphology
 - stem cells
 - behavioral and cognitive researches
 - physiopathology
 - hemadenology
 - immunology
 - biochemistry
 - oncogerontology
 - nutrition
 - pharmacology and toxicology
 - phytoogerontology
 - physical culture
 - ecological gerontology
 - mathematical method and statistics
4. Scientific and Clinical Division
Department of Preventive Gerontology
Departments of:
 - Cardiology
 - Pulmonology

- Nephrology
- Prostate Gland Study
- Psychogeriatrics
- Orthopedics and traumatology
- Ophthalmology
- Cosmetology and anaplasty
- Audiology
- Day patient facility
- “Alarm button”
- Hospice

5. Scientific-Organizational Division

- Analytical laboratory (search and analysis of scientific literature)
- International Relationship Group
- Editorial and Publishing Group
- Scientific Library

6. Production Division

- Synthetic peptide drugs plant
- Organic Synthesis Laboratory

7. Research and Technology Division

Section 9

IDENTIFICATION OF THE MOLECULAR MARKERS IN AGING

SELECTED CLAUSES

According to common definition – aging biomarkers are the biological parameters of an organism, which independently or in a complex combination, define the functionality of an aging organism better than its chronological age.

Potential biomarkers of aging should meet the following conditions:

1. To predict the results of the wide range of aging tests (biochemical, physiological and behavioural) and to do it better than the chronological age.
2. To predict the remaining life expectancy of the individual, designating the age in which about 90% of such a population would remain alive. The accuracy of the prediction should consider the possibility of the most widespread illnesses connected with aging occurring.
3. The procedure for biomarker measurement should not influence the expected life expectancy.

Probably, biomarkers with good accuracy should not only reflect the changes connected with the advancement of years, but also any degenerate processes occurring in an organism. The overall target is to learn to define how the organism's physiological functions will work over the course of aging. Finally, the aging biomarkers will be used for developing medicines, or other agents for slowing down the process of aging and increasing general life expectancy.

There are objective obstacles when searching for informative biomarkers on aging:

1. The mechanisms of aging are not well known yet. There are dozens of hypotheses differently explaining the aging phenomenon.

2. The variation of biological parameters between individuals and the discrepancies during value- measurement. These fluctuations can be large enough to blur the distinctions between the measured parameters.

3. The overlapping of aging events and the occurrence of illnesses. The risk of the development of many diseases which, in turn, can influence the aging process, increases through the years.

4. It is not clear yet on how to classify age changes: it is not known which of them are significant, and which indicate irreversible age changes and which ones can be ignored. It is also not known where the threshold borders lie for different age changes at which their crossing causes considerable and critical changes in the organism to occur.

5. Insufficient financial support of the work connected with the search of aging biomarkers.

Work on the search for aging biomarkers should include full-scale interdisciplinary research with the participation of laboratories in different countries. As an example of the organization of similar research we can show the European project on the identification of longevity genes "Genetics of Healthy Aging (GEHA)", uniting the effort of scientists in European countries and in China.

A priority research goal is in the identification of the set of aging biomarkers for humans and animals.

The primary goals of the research:

1. To verify the already known parameters changing with the years as possible aging biomarkers for humans and animals.
2. To experimentally find an optimum combination of aging markers which satisfy the above-stated definition of an aging biomarker. A priority direction in the given problem is in the definition of an aging biomarker for humans.
3. To search for new aging biomarkers

9.1. PROCESSING THE INFORMATION CONCERNING PREVIOUSLY DISCOVERED AGING BIOMARKERS

The purpose – the definition of applicants in the role of aging molecular markers and the kinds of model organisms used for the task's performance.

9.1.1. A quantitative estimation of the correlation factor between the age of animals and potential aging biomarkers which result in the necessity to choose model animals (it is offered to use mammals, preferably those which have a completely sequenced genome).

9.1.2. Comparative research into animals with «negligible» aging and their close relatives (for example, the naked mole rat *Heterocephalus glaber* which has a life expectancy of 25-28 years, and the closely related shrewmouse which only lives for 2-3 years), which can help not only finding out about aging biomarkers, but also identifying the distinctions between aging programs.

9.1.3 Studying potential aging biomarkers

- 9.1.3.1. The length of telomere and telomerase
- 9.1.3.2. Oxidizing damage to DNA (8-oxoguanine), proteins (for example, carbonylation) and lipids (malondialdehyde and 4-hydroxynonenal)
- 9.1.3.3. Deletion of mitochondrial DNA (so-called «common deletions», most often occurring in brain excitators);
- 9.1.3.4. Genomic DNA mutation
- 9.1.3.5. DNA methylation, changing the promoters' activity
- 9.1.3.6. Level of DNA reparation
- 9.1.3.7. Gene expression profiling;
- 9.1.3.8. Histons' phosphorylation
- 9.1.3.9. Activity of some enzymes (beta-galactosidase, glycolysis enzymes, mitochondrial electron transport chain);
- 9.1.3.10. Cell response to stress (e.g. heat shock proteins);

- 9.1.3.11. Pro-inflammatory cytokines (IL-6, TNF- α , IL-1 β) and hormones (growth hormone, thyroid-stimulating hormone, insulin growth factor 1), and also tissue sensitivity to them.
- 9.1.3.12. Antioxidative status on the cellular and organism level, activity of antioxidative enzymes: thioredoxin, peroxiredoxin, superoxide dismutase, level of apolipoproteins in blood serum;
- 9.1.3.13. Histological changes
- 9.1.3.14. Physiological and psychological functions

9.2. RESEARCH INTO THE CHOSEN MODEL ANIMAL AND POTENTIAL AGING BIOMARKERS

9.2.1. Carrying out research on the measurement of the chosen parameters complex – potential biomarkers of the aging model in animals – with the following features:

- A great quantity of investigated parameters on the same kind of the animal, which are received as the result of noninvasive and invasive research methods;
- Parameters are defined as being those with intervals of 10-20% from the average life expectancy that will allow receiving a detailed picture of age changes;
- A great number of experimental animals (from 1000 for each kind) that will provide high reliability of the received results;
- The independent statistical analysis of the received data for each kind of animal and a comparison of the aging biomarkers of the organisms with negligible aging and their genetically close relations to such features.

9.3. FULL-SCALE RESEARCH ON THE CHOSEN PATIENTS, WITH THE USAGE OF NONINVASIVE METHODS THROUGHOUT ALL THEIR LIFE

9.3.1 Attraction of a considerable quantity (ten thousand) healthy volunteers from the age of 20 to 80. It is desirable, that there are enzymotic

twins participating the in research, including families with long lived relatives.

9.3.2. Gathering the preliminary information of the health status for each patient:

- 9.3.2.1. Behavioral, psychological, physiological, biochemical and genetic tests;
- 9.3.2.2. Characteristics as to the life of the individual, not only including especially genetic and medical data, but also social and demographic facts.
- 9.3.2.3. Full sequence of the each examine genome, or, at least, the analysis of the polymorphism of the individual nucleotide replacements (SNP).

9.3.3. Measurement of presumable aging biomarkers by means of noninvasive procedures which are limited by experiments with blood samples, physiological tests and measurements, including nuclear magnetic resonance and positron emission tomography, and also, probably, biopsy of skin, muscles and fatty tissue.

9.3.4. Performing repeated research throughout the whole life of the examinees with an interval of 3-5 years

9.3.5. In the case of the patient's death, an exact establishment of its reasons and furthermore – their classification

9.3.6. Analysis of the research results by means of multidimensional logistical regression.

9.4. USE OF THE MOST UP TO DATE SCIENTIFIC AND TECHNICAL DEVELOPMENTS IN THE FIELD OF GENOMICS AND PROTEOMICS FOR THE PURPOSE OF IDENTIFYING NEW AGING BIOMARKERS

9.4.1. Studying the possibility using the data about changes in the protein quantity or RNA in different tissues as aging biomarkers.

9.4.2. Searching for protein aging biomarkers with the development of corresponding methods of proteomic analysis.

9.5. ACCOMPANYING RESEARCH ON A SEARCH FOR AGING BIOMARKERS

9.5.1. Fundamental work in the field of research of an aging phenomenon on the cellular and organism level.

9.5.2. Improvement in research methods.

9.5.2.1. Realization of the “lab on a chip” concept, allowing simultaneous measurement of numerous molecular and biochemical parameters of cell and tissue samples.

9.5.2.2. Developing techniques allowing one to estimate the cellular structure and functional condition of the cells in the tissue by noninvasive way, in vivo.

9.5.2.3. Developing a mathematical apparatus for the analysis of the results on search of the aging biomarkers.

Section 10

MATHEMATICAL MODELLING OF THE LIFE SPAN, LONGEVITY AND AGING

MAIN RESEARCH DIRECTIONS

All classic theories of aging have a lot of in common being different in postulation of reasons and accenting any given aspects of senescence. Mathematical modeling allows the comparison of different theories, singling out their common positions and verifying their conformity with the contemporary data on aging and macrobiosis.

There are two positions, based on which the aging of an organism's physiological systems should be considered: the system (the structure) itself should be described in detail as well as its behavior (function).

At present there are a lot of models that describe the functioning of physiological systems in steady conditions (work in the "fast" time). However, there are practically no models that would consider the behavior of these systems in "slow" time (the aging processes).

The goal of this modelling is to analyze the aging of the concerned systems as well as to obtain a basis for building their models within the framework of the natural technologies conception. It was suggested by the academician A.M. Ugolev and is a system and biological basis for the mathematical modeling of the aging processes. Within the framework of this conception, an organism is considered as being a system, which achieves different life sustaining chains. In biological systems, this is a combination of mechanisms and the means for the transformation of matter, energy and information that ensure an organism's integrity.

A scenario approach will have an important position in the modeling of the aging

processes as it allows one to perform a multi-version situation analysis of the aging process including death. On the one hand, the scenario connects the changes of external conditions; on the other hand, it connects the changes of the proper variable systems. The scenario approach within the natural technologies conception could be applied to the prediction of the organism's system-behavior and for a definition of the life-span of a person under any given ecological, social and economic conditions.

In order to model the length of an active life, there many-stage demographic models could be used, Markov and semi-Markov models, and models with an indistinct logic. These models consider different levels of breakdown from complete health to death. The models differ in the characteristics of the laws of transition between the states and in the principles of referring of an individual to specific states.

Aging, the length of life, and changes in health conditions are exposed to many uncontrollable factors and are described as random processes which could be studied only in view of their mass display, i.e. in view of the studying of groups of individuals and populations. At that, it is quite essential to take into account the specific character of the statistical data being collected and the specific properties of a population.

Obviously, a purposeful full-scale scientific and research program is needed for a comprehensive study of the aging process with the help of a mathematical modeling method.

10.1. MATHEMATICAL MODELING OF FUNDAMENTAL MECHANISMS OF AGING

10.1.1. Analysis of control processes in biological systems as the key to understand the aging phenomenon:

- 10.1.1.1. Elaboration of mathematical models to explain the phenomenon of aging as a result of control in complex biological systems;
- 10.1.1.2. Investigation of protecting systems in the organism from the point of view of development and prevention of aging
- 10.1.1.3. Analyzing the role of mentality in regulation of the processes in human organism;
- 10.1.1.4. Modeling of the regulatory and protection systems of an organism (nervous, immune systems etc.);
- 10.1.1.5. Mathematical analysis of phenomenon of prolonged longevity from the point of view of life support regulation (correlation of parameters, liability to diseases, vulnerability).

10.1.2. Modeling of the normal and pathological aging:

- 10.1.2.1. Modeling the influence of allostatic load on aging and survival processes;
- 10.1.2.2. Modeling of changes in proteins and accumulation of oxidative modifications of macromolecules;
- 10.1.2.3. Modeling of aging in "healthy" organisms;
- 10.1.2.4. Modeling of the «age-specific» morbidity:
 - 10.1.2.4.1. The role of the age-specific and chronic diseases in the contraction of the life span as against the predicted one.
- 10.1.2.5. Progeria modeling;
- 10.1.2.6. Alzheimer disease modeling.

10.1.3. Aging and optimality of biological systems:

- 10.1.3.1. Mathematical modeling of the evolutionary optimal strategies for

development, reproduction and survival;

- 10.1.3.2. Mathematical modeling of the individual patterns of the evolutionary optimal strategy realization using individual data on reproduction and longevity (eggs laying by drosophilas);
 - 10.1.3.3. Modeling of macrobiotic species nascency as a consequence of individual peculiarities of recourses distribution;
 - 10.1.3.4. Modeling of individual and population mechanisms of reproductive and post-reproductive distribution of resources from the point of view of optimal longevity.
- ### 10.1.4. Modeling of reaction of an organism on the environment, and the role of the reactions in aging process:
- 10.1.4.1. Modeling of a cryogenic effect on a cell;
 - 10.1.4.2. Modeling of cryogenic effects on the whole organism;
 - 10.1.4.3. Modeling of the physiological adaptation and aging;
 - 10.1.4.4. Modeling the results of weak external influence on living organisms;
 - 10.1.4.5. Modeling of decline with age in adaptation performance;
 - 10.1.4.6. Modeling for comparative analysis of aging characteristics in changing environment.

10.1.5. Evolution aspects of aging:

- 10.1.5.1. Mathematical justification of the link between aging and optimal evolution strategies;
- 10.1.5.2. Mathematical modeling of the artificial selection for life span prolongation:
 - 4.1.5.2.1. Evaluation of the natural selection optimality;
 - 4.1.5.2.2. Verification of the optimality hypothesis in the artificial selection.
- 10.1.5.3. Interrelation of evolution and human mind (consciousness as a product of evolution, consciousness as a mechanism of evolution).



10.1.6. Mathematical models of aging of the physiological systems in organisms:

- 10.1.6.1. Modeling of the nervous system aging processes
- 10.1.6.2. Modeling aging in brain
- 10.1.6.3. Modeling of aging in regulatory systems in the organism
- 10.1.6.4. Modeling of age-dependent senescence in the organism energetics
- 10.1.6.5. Modeling of cells division and morphogenetic process
- 10.1.6.6. Modeling of subcellular transport processes (penetration of proteins through a membrane, light transport, active transport)
- 10.1.6.7. Modeling of the role of cellular processes in aging
- 10.1.6.8. A model of the virtual aging tissue
- 10.1.6.9. Modeling of the ontogenesis control system
- 10.1.6.10. Modeling bone marrow and hemopoietic system aging
- 10.1.6.11. Modeling aging in heart and vascular systems
- 10.1.6.12. Mathematical model of reproductive system's aging
- 10.1.6.13. Mathematical model of the hormonal system's aging
- 10.1.6.14. A virtual model of an aging organism:
 - 10.1.6.14.1. Mathematical model for aging in nematode C.elegans;
 - 10.1.6.14.2. Mathematical model for aging in nematode C.elegans;
 - 10.1.6.14.3. Mathematical model for aging in humans.

10.2. MATHEMATICAL MODELING THE AGING PROCESSES IN THE FRAME OF NATURAL TECHNOLOGY OF THE ORGANISM

10.2.1. Design of the concept to explain aging as a decline in functional capability of the natural technological systems:

- 10.2.1.1. Elaboration of structural models of the natural technologies combinations in living organism;
- 10.2.1.2. Determination of optimal dimension of the natural technology system for the purpose of mathematical modeling of aging;
- 10.2.1.3. Development of integrated model for homeostasis;
- 10.2.1.4. Development of the conception of "natural death" in the model of natural technology;
- 10.2.1.5. Development of cell processes model in the frame of natural technologies

10.2.2. Modeling of the organism's separate systems as the essential elements of the natural technologies system:

- 10.2.2.1. Gastrointestinal tract ;
- 10.2.2.2. Pulmonary system;
- 10.2.2.3. Kidneys;
- 10.2.2.4. Liver;
- 10.2.2.5. Marrow (hemopoietic system);
- 10.2.2.6. Circulation of the blood;
- 10.2.2.7. Immune system;
- 10.2.2.8. Central and peripheral nervous systems;
- 10.2.2.9. Thermoregulation;
- 10.2.2.10. Hormonal system.

10.2.3. Modeling of the integrant connections in the system of the natural organism's technologies:

- 10.2.3.1. Modeling of the homeostasis block as a central element joining the processes of the natural technologies;
- 10.2.3.2. Modeling of the interdisciplinary aging /homeostasis and homeostasis/ aging interfaces;
- 10.2.3.3. Homeostasis modeling.

10.2.4. Scenario modeling of aging and death within the frame of the natural technology:

- 10.2.4.1. Verifying the results of the modeling according to the data from the aging and the life span of a human being (Tula, Yekaterinburg, Moscow);
- 10.2.4.2. Calculation of the longevity projection for different scenarios of change



in ecological situations in different regions of Russia;

- 10.2.4.3. Construction of the prognosis on the life span in different regions of Russia.

10.3. MATHEMATICAL MODELING OF LONGEVITY

10.3.1. Development of mathematical models for forecasting expected life span:

10.3.1.1. Animals:

10.3.1.1.1. Development of mathematical models to forecast life span in Drosophila;

10.3.1.1.2. Development of mathematical models to forecast life span in fruit flies: Medfly and Mexfly;

10.3.1.1.3. Development of mathematical models to forecast life span in mice and rats.

10.3.1.2. Humans:

10.3.1.2.1. Definition of genetic determinants;

10.3.1.2.2. Clarification of the impact of environment and health care in changes of life span.

10.3.2. Mathematical models for healthy life span: (many-stage models, Markov models, models with an indistinct logic)

10.3.2.1. Animals:

10.3.2.1.1. Mathematical models that include disabilitation in form of supine behavior;

10.3.2.1.2. Development of age-specific biological indexes (behavioural, physiological).

10.3.2.2. Humans:

10.3.2.2.1. Development of age-specific biological indexes;

10.3.2.2.2. Mathematical modeling of biological age;

10.3.2.2.3. Mathematical modeling of "diseases of aging";

10.3.2.2.4. Mathematical modeling of disabilitation;

10.3.2.2.5. Mathematical modeling of invalidisation

10.3.3. Modeling of action on organism to prolong life span:

10.3.3.1. Electric and magnetic fields action at brain to increase life span;

10.3.3.2. Pharmacological action aimed to increase life span (proteomics);

10.3.3.3. Sub-cellular action to increase life span (Skulachev ion);

10.3.3.4. Cryogen action on organism to increase life span;

10.3.3.5. Action of stress;

10.3.3.6. Hormesis effect;

10.3.3.7. Analysis of relationship between stress resistance and longevity in laboratory animals and humans;

10.3.3.8. Freezing effects;

10.3.3.9. Modeling the role of caloric restriction and dietary restriction in longevity;

10.3.3.10. Modeling the role of reproduction restriction in longevity;

10.3.3.11. Modeling of role of genetic modifications;

10.3.3.12. Modeling the influence of living conditions, ethnic and religious conditions on longevity (Indians Ache, sect of gutterits, marmons and other);

10.3.3.13. Geroprotector effects; (melatonin, peptides and so on);

10.3.3.14. Analysis of radiation effects;

10.3.3.15. Analysis and modeling of little influences on the human being organism.

10.3.4. Analysis and modeling of changes in human longevity in historical perspective:

10.3.4.1. Modeling of changes in longevity using paleodemographic data, construction life tables;

10.3.4.2. Modeling and analysis of the radical increase in longevity from ancient times till our days.



10.3.5. Analysis and development of existing mathematical models of longevity (critics, revelation of advantages and disadvantages):

- 10.3.5.1. Mathematical models of species specific longevity phenomenon;
- 10.3.5.2. Development of the classical mathematical models for longevity in the case of heterogeneity;
- 10.3.5.3. L. Piantanelli approach;
- 10.3.5.4. Homeostatic approach of V.N. Novoseltsev;
- 10.3.5.5. Other approaches.

10.4. DEVELOPMENT OF METHODOLOGY FOR MODELING PROCESSES OF AGING, LOSS OF HEALTH AND LONGEVITY

10.4.1. Application of different mathematic approaches to longevity modeling:

- 10.4.1.1. Balance models (models of T. Penna, Pletcher-Noyhauser) and their development;
- 10.4.1.2. Models of reliability theory (of V. Koltover, models of L. and N. Gavrilovuh, M. Nikulin) and their development;
- 10.4.1.3. Heterogeneity (approach of A.I. Jashin, A.I. Mihalskij);
- 10.4.1.4. Stochastic modeling;
- 10.4.1.5. Energy homeostatic approach;
- 10.4.1.6. Oxygen homeostatic models (V.N. Novoseltsev approach);
- 10.4.1.7. Population aging models;
- 10.4.1.8. Synergetic models (approach of G.G. Malinetskij);
- 10.4.1.9. Interdisciplinary modeling (V.N. Novoseltsev approach).

10.4.2. Construction of mathematical models which account for uncertainty in structure and parameters of aging and longevity:

- 10.4.2.1. Adaptation of modern methods of data analysis under uncertainty and partial observability of aging and loss of health processes.

- 10.4.2.2. Development of formal stochastic aging models.

10.4.3. Identification of mathematical models on incomplete data:

- 10.4.3.1. Formulating the requirements on amount and quality of information needed for identification of mathematical models of aging.
- 10.4.3.2. Experimental estimation of exactness of received models according to simulated data.

10.4.4. Development of the methods of experiment design for investigation of longevity in model organisms:

- 10.4.4.1. Longevity modulation by dietary restriction;
- 10.4.4.2. Influence of stress on aging and longevity;
- 10.4.4.3. Role of reproduction restriction on longevity;
- 10.4.4.4. Life span increase by implementation geroprotectors.

10.4.5. Development of computer aided methodology for aging modeling:

- 10.4.5.1. Analyses of specialized computer languages and systems for aging modeling (Simula, SBML and other).
- 10.4.5.2. Development of computer models based on evolutionary principles in humans and in animals.

10.5. MATHEMATICAL MODELING AND ANALYSES OF AGING AND LOSS OF HEALTH PROCESSES IN GROUPS AND POPULATIONS

10.5.1. Development of methods exploring specificity of data collection:

- 10.5.1.1. Development of mathematical models of health indicators dynamics (morbidity, risk factors prevalence, aging indicators etc.) to produce the design invariant descriptions.



10.5.2. Analysis of population genetics data:

10.5.2.1. Mathematic modeling for search of genetic determinants of healthy longevity.

10.5.3. Mathematical modeling and analysis of links between chronic morbidity, aging and mortality:

10.5.3.1. Investigate and model the links between chronic morbidity and mortality at advanced ages.

10.5.3.2. Modeling influence of co-morbidity on mortality.

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

10.6.1. Genetic level:

10.6.1.1. Modeling the influence on longevity of expression of genes which are common in humans and laboratory animals.

10.6.1.2. Analysis and modeling the role of evolutionary conservative genes.

10.6.2. Cellular level:

10.6.2.1. Modeling of reparation reactions which protect the living organism from oxidative damage.

10.6.2.2. Modeling of reactions for utilization, production and accumulation of energy at cellular level to explain the species specific longevity.

10.6.3. Subcellular level:

10.6.3.1. Modeling the processes of damage and reparation of proteins.

10.6.4. System level:

10.6.4.1. Modeling homeostasis and homeoclasia in humans and animals.

10.6.5. Adaptation level:

10.6.5.1. Mathematical modeling of the influence of external conditions on laboratory animals' longevity in terms

of adaptation, energy redistribution between main functions of the organism and reaction norms.

10.6.5.2. Modeling the role of influential events at different stages of ontogenesis on longevity of animals and humans.

10.6.5.3. Mathematical modeling of common principals of health loss in animals and humans.

10.6.6. Evolution level:

10.6.6.1. Mathematical modeling and estimation of the limits of life span modification for animals and humans.



Section 11

MICROECOLOGY AND AGING

MAIN RESEARCH DIRECTIONS

11.1. INVESTIGATIONS INTO CHANGES IN “MICROFLORA- ORGANISM” ECOSYSTEM IN THE COURSE OF AGING

- 11.1.1. Research study of microflora proper and changes of the same in the course of aging;
- 11.1.2. Investigations into age-related changes in epithelium interacting with microflora, its frontal systems, such as glycoprotein antigens, lactoferrin, local immunity system (s-IgA);
- 11.1.3. Investigations into age-related changes in pre- epithelium layer, which is a unified integrated system, a matrix including bacterial glycocalyx, exposed glycoproteids of epithelial cells, epithelial polysaccharide polysaccharides with distribution of low-molecular metabolite of different origin, mineral and organic ions in this matrix.
- 11.1.4. Investigations into age-related changes in composition and quality of mucus as microflora environment
- 11.1.5. Investigations into age-related changes in the state of barrier body tissues, including the behavior of specific receptors for bacteria
- 11.1.6. Investigations into age-related changes in metabolic activity of gastrointestinal microflora
- 11.1.7. Investigations into age-related changes in output of bioactive

compounds by microorganisms (vitamins, hormones, antibiotics, toxins, etc.)

11.2. INVESTIGATIONS INTO THE INFLUENCE OF RISK FACTORS ON THE STATE OF “HUMAN ORGANISM-NORMAL FLORA” SYSTEM:

- 11.2.1. medical diseases, primarily gastrointestinal diseases;
- 11.2.2. stresses, especially chronic;
- 11.2.3. diet faults (irregular and/or nutrients-unbalanced diet);
- 11.2.4. acute infectious diseases of gastrointestinal tract;
- 11.2.5. iatrogenic effects:
 - 11.2.5.1. antibacterial therapy;
 - 11.2.5.2. hormonotherapy;
 - 11.2.5.3. use of cytostatics;
 - 11.2.5.4. radiation therapy;
 - 11.2.5.5. surgery;
- 11.2.6. xenobiotics of different origin;
- 11.2.7. biorhythm disorders;
- 11.2.8. excessive background radiation;
- 11.2.9. magnetic disturbances.

11.3. RESEARCH STUDY OF AGE-RELATED CHANGES IN INTERACTION OF MICROFLORA AND ORGANISM IMMUNE SYSTEM

- 11.3.1. Research study of “mutual molecular mimicry” phenomenon (microorganisms’ procurement of receptors and antigens indigenous to a macroorganism and vice versa), depending on age.
- 11.3.2. Research study of modulating action of gastrointestinal microflora on output of cytokines with a wide range of biological action.
- 11.3.3. Research study of participation of bacterial modulins (histamine,

thrombotonin, prostaglandins, leukotrienes, free radicals, platelet-activating factor), in regulation of hemodynamic parameters of microcirculation in various organs, of blood coagulability and flow properties, hormones synthesis, pulmonary ventilation.

- 11.3.4. Research study of action of microbial metabolites and metabolites mediators on modulation of proliferation, cytodifferentiation, apoptosis and metabolic reactions of eucariotic cells at cellular and tissue level.
- 11.3.5. Research study of age-related bacterial population changes that lead to abnormality of "microflora-organism" links whereby the organism conceives its own bacteria as immunologically extraneous bacteria.

11.4. RESEARCH STUDY OF MOLECULAR INTERACTIONS BETWEEN ORGANISM AND ITS MICROFLORA IN THE COURSE OF AGING:

- 11.4.1. metabolism-participating low-molecular particle elements of various classes;
- 11.4.2. oligomeric molecules and supermolecules that not only migrate but mediate direct contacts of bacteria among each other and eucaryotes;
- 11.4.3. complex supermolecular structures (desquamated epithelium cells, bacterial cells, organellas, big toxins, etc.);
- 11.4.4. hypercomplex formations of pre-epithelium layers type, contact area wherethrough communications between the host and microbiota occur;
- 11.4.5. physico-chemical parameters conditioning homeostasis of contact areas, i.e. local acid-base, capacitance, oxidation-reduction, rheologic, buffered characteristics;
- 11.4.6. processes, kinetics of the same, both chemical and physical;

- 11.4.7. 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.

Section 12

REPRODUCTION AND AGING

SELECTED RESEARCH DIRECTIONS

12.1. STUDY OF AGE-DEPENDENT ALTERATIONS OF REPRODUCTION AND METHODS OF ITS CORRECTION:

- 12.1.1. Sex hormones disbalance;
- 12.1.2. Libido decrease;
- 12.1.3. Mutations and chromosome aberrations in germ cells;
- 12.1.4. Apoptosis of germ cells.

12.2. RESEARCH OF THE MECHANISMS OF ANTAGONISM BETWEEN REPRODUCTION AND LONGEVITY:

- 12.2.1. Endocrine influence on somatic tissues;
- 12.2.2. Redistribution of resources from soma to germ;
- 12.2.3. Behavior expenditures for reproduction.

12.3. TWO-WAY INFLUENCE OF MALES AND FEMALES WITH CONNECTION TO LONGEVITY:

- 12.3.1. The influence of males on females life span;
- 12.3.2. Maternal effect.

12.4. THE ANALYSIS OF THE MECHANISMS OF SEX DIFFERENCES IN LIFE SPAN:

12.4.1. Social component:

- 125.4.1.1. Detection of genetics reasons of behavior risks in males.

12.4.2. Biological component:

- 12.4.2.1. Heterogametic and homogametic sexes;
- 12.4.2.2. Neuroendocrinal regulation of differences between sexes;
- 12.4.2.3. Telomere truncation speed with connection to sex;
- 12.4.2.4. Differences of antioxidant capacity between sexes;
- 12.4.2.5. «Grandmother effect».

Section 13

ENVIRONMENTAL INFLUENCE ON AGING

SELECTED RESEARCH DIRECTIONS

13.1. OXIDATIVE STRESS AND AGING:

- 13.1.1. The rate of living theory verification;
- 13.1.2. The influence of oxygen pressure on longevity;
- 13.1.3. The reactive oxygen species involvement in normal ontogenesis, hormesis and aging.

13.2. INFLAMMATION AND AGING:

- 13.2.1. Inner immunity alteration during aging;
- 13.2.2. Acquired immunity changes during aging;
- 13.2.3. The pathways of chronic inflammation in aging cells.

13.3. THE INFLUENCE OF DIET ON LIFE SPAN:

- 13.3.1. Caloric restriction;
- 13.3.2. Quality composition of diet for longevity.

13.4. TEMPERATURE AND AGING:

- 13.4.1. The mechanisms of temperature influence on aging speed;
- 13.4.2. Temperature-induced hormesis;
- 13.4.3. Heatshock proteins in anti-aging.

13.5. LIGHT REGIMES AND AGING:

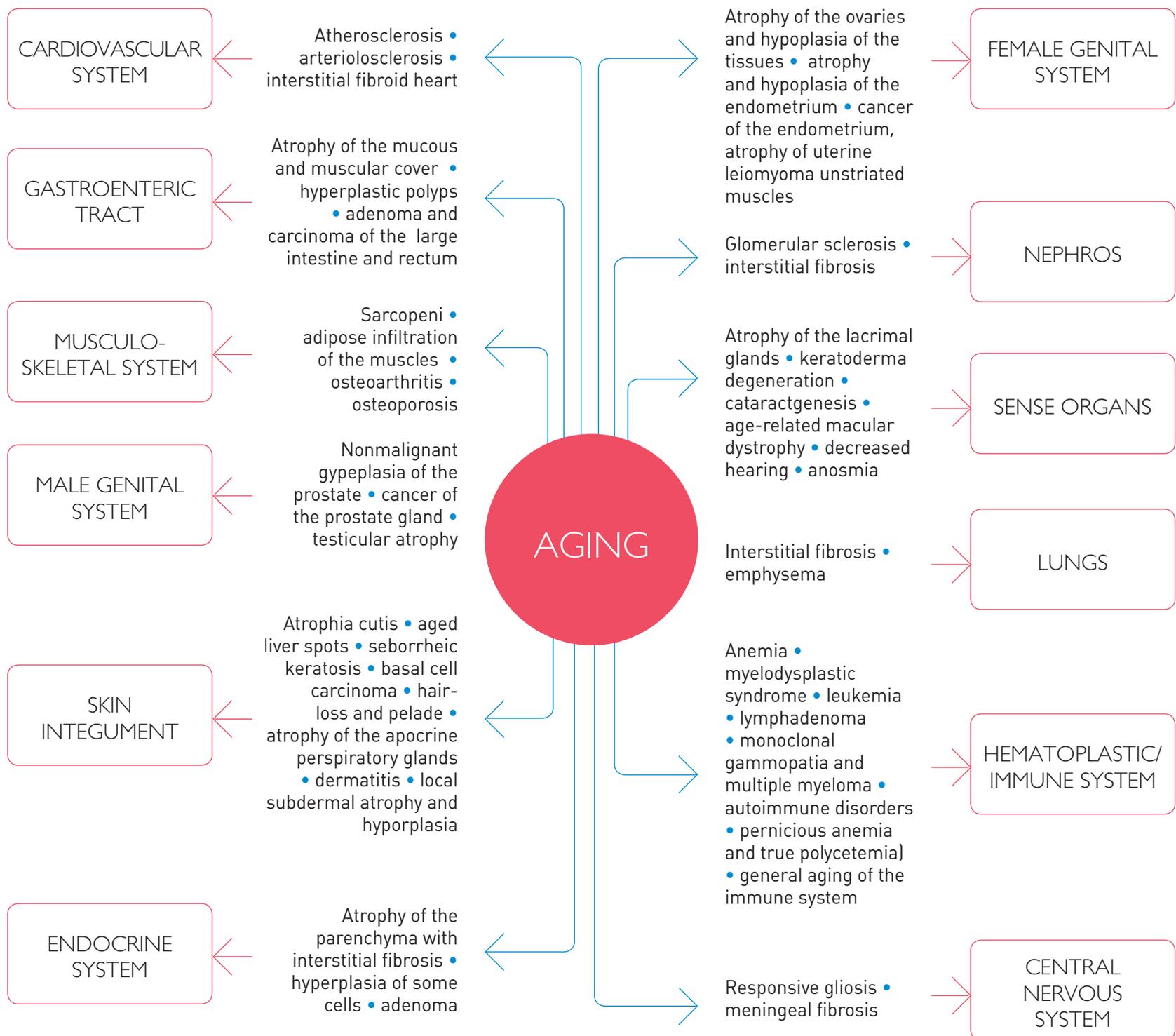
- 13.5.1. Intensification of vital activity at light as aging-accelerating factor:
 - 13.5.1.1. Reproduction activation;
 - 13.5.1.2. Change of ratio between rest and activity.
- 13.5.2. Suppression of neuroendocrinal regulation in dark regime.

13.6. IONIZING RADIATION AND AGING:

- 13.6.1. Radiation hormesis;
- 13.6.2. Radiationadaptive response;
- 13.6.3. Hyper-radiosensitivity and aging acceleration;
- 13.6.4. Radiation-induced oncogenesis. Hypergravity and life span.

ONCE AGAIN, WE WISH TO HIGHLIGHT THE IMPORTANCE OF A COMPLEX STUDYING OF THE AGING PROCESSES SINCE AGING IS THE REASON AND THE LATENT STAGE FOR PATHOLOGICAL PROCESSES IN THE MAJORITY OF TISSUES AND ORGANS

BREACHES TO THE PROLIFERATE HOMEOSTASIS IN THE PERSON'S AGING
(Martin, 2007)



DEAR COLLEAGUES!

WE WOULD BE GRATEFUL IF YOU COULD FIND TIME TO EXPRESS YOUR EXPERT OPINION ON SOME QUESTIONS CONCERNING THE PROGRAM «SCIENCE AGAINST AGING»:

1. Please, express your opinion on the offered approach to the ordering of materials for the program according to the structure stated on pages 8-9.
2. Please, answer 12 basic questions on the biology of ageing, formulated on p. 9 (the last column to the offered structure of the program «Science Against Aging»).
3. Give your opinion on the ordering of inter-related ageing processes and stress resistance, stated in the diagram on pages 12-13. If possible, make additions, suggestions and updates.
4. Please, inform us if you could take part in the program «Science Against Aging»? If yes, then in what capacity: as an editor, a developer, or an organizer?

We would be very grateful if you could state the comments, remarks, suggestions and additions to any sections of the program «Science against ageing» which have been presented in this booklet. Also, we would welcome your input on those areas which require further development.

YOUR OPINION IS VERY IMPORTANT TO US.
WE ARE ALWAYS OPEN TO DIALOGUE AND WELCOME YOU
WITH THOUGHTS TO ADD!

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