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Different Approaches to Research into the Aging Process and Their Implementation in the Framework of the "Science Against Aging" Complex Interdisciplinary Program

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Abstract—We presume that extending lifespan and particularly its healthy period is absolutely beneficial for human being. However, the existing views and approaches did not result in a significant extension of human lifespan.

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Improved living standards, medical and sanitary measures could only increase the average life expectancy, which was achieved solely by reducing the number of accidental deaths and deaths caused by some pathological conditions and infections. The life-extending effect of the "universal" anti-aging approach of caloric restriction still has not been proven. Neither has it been possible to develop effective biomarkers of aging. In addition to that, the anti-aging treatments available today have a fairly inconsistent effect on human lifespan.

New emerging knowledge has made it clear that gerontology calls for some new approaches. We believe the demand for developing a complex interdisciplinary anti-aging research program has maturated in the scientific community.

Extending the lifespan and especially its healthy period is absolutely beneficial for human being. Gerontologists have long payed special attention to the problem of aging retardation. However, the existing gerontological concepts and approaches have yet not managed to considerably prolong the maximum life expectancy. Improved livinig standards and medical and sanitary measures could only increase the average life exectancy, i.e. reduce the number of accidental deaths and deaths caused by certain pathological conditions and infections. The life-extending effect of a "universal" control of aging processes, involving caloric restriction, has not yet been proven effective for humans. No effective biomarkers of aging have, too, yet been developed. Moreover, the anti-aging drugs available today have a questionable effect on life expectancy. It not infrequently fits in the hormetic zone established for a nonspecific compensatory stress response (20–30%), which casts doubt upon the ability of anti-aging drugs to directly affect the mechanisms of aging. Thus, the existing approaches are insufficiently efficient to provide a considerable increase of the maximum life span and a healthy longevity.

At the same time, there is an avalanche-like increase of evidence for the role of certain genes in life span regulation of model animals and for reproducible changes in the expression of thousands of genes in the aging of different tissues, associated with epigenetic transformations. Fundamental advances in the regenerative medicine (reprogramming differential cells into stem cells, identification of cytokines controlling cell differentiation) have also been achieved.

The emerging knowledge has created demand for alternative gerontological approaches. In our opinion, a necessity in developing an interdisciplinary anti-aging research program has maturated. A methodology for developing this program and its structure, as well as

principles of communication of program participants should be determined. Critical analysis of the existing approaches, ideas, and suggestions is required. Let us consider some of the approaches.

1. "**Priority-based approach**," suggested by repeperesentative of the U.S. Government and leading gerontologists at the Summit of the U. S. National Institute of Aging in September, 2008 (Gaithersburg, Maryland) [1]. This approach consists in setting the following priorities.

– *Search for health quality markers*. Until present the life span was used as the principal parameter of aging slow down. However, in our opinion, to simply extend the lifespan is meaningless and even couterproductive, unless the healthspan is simultaneously extended. Therefore, it is necessary to understand what markers allow assessment of just the healthspan.

– *Studying potential differences in aging of mitotic versus postmitotic cells*. The model organisms used in most of such studies (adult round worms and flies) consisted almost exclusively of postimitotic tissues. The range of models should be complemented by new organisms that are also genetically tractable but having proliferative tissues as adults.

– *Focusing researchers' attention on cellular response to stress*. It was established that the longevity of many organisms is associated with their ability to generate an adequate cellular response to stress.

– *Studying the role of the immune system in aging*. Inflammation plays an important role in a variety of age-related diseases and pathologies. The number of inflammatory cytokines increases with age, which correlates with the susceptibility to various diseases.

– *Using stem cells*. Before stem cells, including induced pluripotent stem cells, will be introduced in the therapy of aging, much effort should be to gain a deeper understanding of the normal biology of stem and progenitor cells in aging.

2. **Engineering approach**. According to the developers of this approach, one can, even not knowing the basic reasons of aging, to slow down this process or even make it negligible by timely "reparing" the damage accumulated with age. This approach is exemplified by the de Grey's Program entitled "Strategies for Engineered Negligible Senescence" (SENS), which recognizes seven types of damages and suggests their treatment schemes [2]. Let us recall the basic postulates of this approach.

– *Replacement of cell loss*. There are three main ways to make up for cell loss. One of them involves natural stimulation of cell division. This is like physical exercises favor build-up of muscle mass. The second way consists in artificial administration of growth factors (for instance via injections) to stimulate cell division. Further on, introduction into the organism of cells modified so that they divide effectively and replenish lost cells.

– *Repairing chromosome aberrations*. Chromosome mutations are more reasonable to prevent rather than repair. The approach suggested by Aubrey de Grey consists in whole-body interdiction of lengthening of telomeres, which will prevent carcinogenesis. However, this will require periodic reseeding of all stem cells.

– *Preventing mitochondrial mutations*. Mitochondrial mutations are better to prevent rather than to repair. Copies of 13 genes coded by mitochondrial DNA are suggested to be made and introduced into nuclear chromosomes.

– *Elimination of accumulated useless cells,* such as fat, senescent, and certain immune cells. A medicine can be developed, which will force useless cells to "commit suicide" but leave untouched other cells. A targeted immune response for doing away with useless cells can be stimulated.

– *Breaking extracellular closs links*. To this end, chemical compounds capable of breaking protein cross links but not affecting other chemical structures in the organism should be created.

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

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

3. **Cancelling the aging program**. Certain researchers suggest existence of the aging program. If this indeed the case, i.e. aging is a programmed process, one should look for this program and develop approaches to intervening in aging processes so that the program is cancelled. Then it will no longer be

necessary to search for and eliminate each of the consequences of aging as proposed in the engineering and priority-based approaches. For example, A. Comfort, A.M. Olovnikov, and others suggest that such an aging program is governed by "biological clocks" whose functioning in the body is controlled by the epiphysis and hypothalamus. However, it is not excluded that there exists no special aging program; instead, a stable quasiprogram [3] or the so-called antagonistic pleiotropy [4] take place, when key genes controlling metabolism, growth, and development of the organism, have long term side effects responsible for aging .

4. Problem-oriented approach. This approach focuses research efforts on the basic problems and issues of aging biology. It favors consolidation of the scientific community via discussing the key issues, developing a common conceptual system, and forming the immortalistic worldview ("a system of ideas based on an aspiration to at most postpone physical death relying on achievements of exact, natural and technical sciences"—*Wikipedia*). To this end, the "Science for Life Extention" Foundation organized a correspondence discussion of questiong concerning aging biology, with the participation of leading Russian and foreign researchers. Below we present examples of such questions and versions on answers on them.

– What is aging?

(1) Enhanced probability of death by biological reasons. (2) Execution of a self-destruct program. (3) Homeostasis disruption at different levels of organization of life as a result of an age-related failure in the functionality of the systems responsible for maintaining the stability of its internal environment.

– Why do organisms experience a progressive and irreversible decrease in their physiological functions at the end of their life?

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

– What are the mechanisms responsible for the differences in life expectancy or the rate of aging within one species and between species?

(1) Differences at different levels of aging regulation (metabolism, stress resistance, tissue regeneration and cell death, and neurohumoral regulation). (2) Differences arising at every new higher level of the organization of living systems during evolution. (3) Different rates of reaching the reproductive age. (4) Different anti-aging programs. (5) Different aging programs.

– Why do experimental impacts like caloric restriction, delay the onset of a number of age-related physiological and pathological changes and increase the average and maximal life span in animals?

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

– Do age-related changes in an organism enhance its susceptibility to diseases or do diseases develop independently and only then exacerbate the effects of aging?

(1) Yes, undoubtedly enhance. (2) There is no aging as such; rather a combination of pathologies takes place. (3) Every organism experiences aging while concrete age-related diseases only develop in some individuals. Therefore, it would be a mistake to equate age-related diseases and the aging process as such.

– What is the evolution stage did aging emerge at or it has accompanied life from the moment that it first appeared?

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

– Whether aging processes are caused by aging at the cellular level?

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

– What is the extent to which aging is determined by genes?

(1) Aging is completely determined by genes. (2) Aging is determined by external environmental factors and stochastic causes while the genotype

plays a less prominent role. (3) The environment and genotype are equally important for aging. (4) Aging results from the predominant control and regulation of ontogenesis shifting from the genetic to the systems level after the organism reaches its reproductive age.

– What is the reason for the existence of species with negligible aging?

(1) They lack aging programs. (2) Stress resistance mechanisms in these species are maximized while they are under no natural selection pressure in favor of early reproduction. (3) No such species exist. (4) Such species have radically different anti-aging programs.

– How are reproduction and lifespan interrelated?

(1) There is inverse correlation between lifespan and reproduction (antagonistic pleiotropy and disposable soma theories). (2) It depends. In one cases they correlate with each other anв in other cases not. (3) Sex hormones are one of the main regulators of programmed cell death.

Other answers are possible. We believe this scope of questions needs to be detalized to an extent at which it can be verified in experiments. This could allow us to develop an "agenda" of unsolved problems of aging biology.

The concept of identifying general regularities (proposed by A. Ryazanov) can form a part of the problem-oriented approach. It is based on accumulating proven, verified facts in biology of aging. In waht follows we suggest an example list for discussion and complementation.

(1) Organisms and somatic cells accumulate damage and undergo aging while functional germ cells do not undergo aging.

(2) The probability of death increases with age in accordance with the Gompertz Law. Very old individuals represent an exception to this rule.

(3) There is a species-specific rate of aging. The probability of death for humans doubles every eight years; very old individuals represent an exception to this rule.

(4) There are organisms that do not undergo aging. The probability of death in such organisms does not increase with age.

(5) The pressure of natural selection decreases with age.

(6) Accumulation of protein damage occurs exponentially with age and follows the same law in various organisms.

(7) In various young organisms and in different organs of young organisms the level of protein damage is approximately the same.

(8) There is no convincing data demonstrating that the consumption of antioxidants can affect the rate of aging.

(9) No substances have been identified yet that can substantially slow down the rate of aging or significantly extend the lifespan of mammals.

(10) There is a correlation between the size of an organism and the length of its lifespan. As a rule, larger organisms live longer.

(11) Within species, the opposite correlation: smaller organisms live longer.

(12) It is shown that the accumulation of mutations in the mitochondria shortens lifespan but does not affect the level of oxidative stress in mice.

(13) There are examples when a significant increase in oxidative stress in mammals does not shorten the lifespan. No genes have been found in mice, activation or inactivation of which increase the maximal lifespan beyond the maximal lifespan of wild mice.

(14) The only universal way to increase maximal lifespan of an organism is to subject it to caloric restriction.

(15) Adverse conditions and poisons at very low doses can sometimes increase lifespan.

(16) There is a correlation between the body mass, the rate of metabolism, the rate of protein turnover, and the concentration of mitochondria and ribosomes. The amount of cycles or protein renewal during lifespan is approximately the same for various organisms.

(17) In most organisms, there is an accumulation of lipofuscin in cells and tissues with age.

(18) Werner syndrome displays a lot of similarities to normal aging. Although the mutation that causes this syndrome has been identified, there is no explanation for this phenomenon.

(19) Telomerase deficiency does not affect the lifespan of mice.

(20) In most cases, cancer is accompanied by chromosomal aberrations.

(21) The incidence of cancer, Alzheimer's, and diabetes increases with age.

(22) As a rule, the rate of metabolism and protein turnover decreases with age.

(23) The lifespan of nematodes can be increased several-fold through the mutation of some genes.

(24) Aging is not directly related to the limited number of cell divisions.

(25) With age, there is a decrease in resistance of cells to stress and an increase in the probability of apoptosis.

(26) Mutations that increase cellular resistance to stress and apoptosis, in some cases, may lead to an increased lifespan in mice.

(27) The regenerative potential of stem cells decreases with age.

(28) As a rule, females live longer than males.

5. Development of a unified synthetic theory of aging in the evolutionary comparative aspect. The unified theory should consider numerous factors, the most important of which are evolution and comparative biology. This theory can, for example, be represented by a set of schemes and tables describing the aging processes at different levels of organization of life for different types of tissues (proliferative, postmitotic) and for different types of animals, with account for the evolutionary aspect.

6. "**Search method.**" There is a suggestion to screen 100 000 chemical compounds on mice in order to reveal their geroprotective properties (the search method). The authors of this idea start from the assumption that simple screening would lead to a positive result faster than actions based upon analytical work, due to the lack of knowledge and understanding of human metabolism.

Developing the "Science Against Aging" Complex Interdisciplinary Program, the "Science for Life Extension" Foundation presumed that all the above-listed approaches most likely do not contradict each other and should all be taken into account, addressing the problem in different ways. We also suggest defeating aging to be considered as not only a research but as a technological problem in the first place.

Thus, the "Science Against Aging" Program suggests a total approach comprising several methodical problems and approaches actualized in the program. Their simultaneous implementation can be organized in the following lines of activities.

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

2. *Studying aging and stress resistance mechanisms in model animals***.** At present gerontology is going through a stage of intensive data collection. At this stage it is necessary to take inventory of the ideas about the nature of aging that are available today and to test these ideas experimentally. While research into systemic changes must continue (changes at the level of cytokines, hormones, metabolites, damaged structures), special attention has to be paid to tissue specific features of aging and stress resistance as well as to the difference in aging of stem cells, proliferative cells and postmitotic somatic cells.

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

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

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

6. *Developing methods for evaluating and predicting the biological age and the effectiveness of therapies.* No therapy, whether it is based on genetic engineering, environmental modifications or the use of drugs, can be applied adequately unless there are methods for evaluating its effectiveness. For this purpose new precise biometrics need to be found to evaluate the aging process and the biological age of an individual. Eventually a system of differential equations will have to be developed that would make it possible to predict the effectiveness of any type of interference in the aging process.

7. *Developing technologies for interfering in the aging and anti-aging processes.* Once key points for interference have been identified and methods for assessing the effectiveness of interference have been developed the next stage will be to develop specific technologies for interfering in the aging and anti-aging processes, which would eventually lead to development of therapies that will increase both life span and healthspan of human beings.

Thus, the "Science Against Aging" Complex Interdisciplinary Program has been developed to coordinate individual effort of different groups of researchers who deal with different aspects of aging at the molecular, sub-cellular, cellular, organ, system, and population levels in their biochemical, genetic, environmental, demographic, and medical studies. The implementation of the total approach will make it possible to model aging processes at different levels of integration of biosystems and develop a set of practical measures aimed at cancelling aging.

We invite experts for collaboration in developing an anti-aging strategy.

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