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REVIEW ARTICLE

Biogerontology in Russia: from past to future

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Abstract The paper presents major steps of gerontology development in Russia. The issues of training in gerontology and geriatrics, institutional infrastructure within the Gerontological Society of the Russian Academy of Sciences and its activities have been considered therein. Some results of Russian researchers obtained during 2005–2010 have been summarized as well. Special attention is given to the prospects of gerontology in Russia.

Keywords Aging research · Biogerontology · Main results · Russia

Abbreviations

IBCP	N.M. Emanuel Institute of Biochemical Physics, RAS
ICP	Institute of Chemical Physics, RAS
IGC	Institute of Genetics and Cytology, Siberian Branch of the RAS
IPCB	A.N. Belozersky Institute of Physical and Chemical Biology
IPCP	Institute of Problems of Chemical Physics, RAS
RAMS	The Russian Academy of Medical Sciences
RAS	The Russian Academy of Sciences
RIEM	Research Institute of Experimental Medicine, RAMS
RIOG	D.O. Ott Research Institute of Obstetrics and Gynecology, RAMS
SMC-CVSRS	Scientific-Medical Center of the Committee of Veterans of Special Risk Subdivisions in Russian Federation
SPb	Saint-Petersburg
SPb IBG RAMS	St. Petersburg Institute of Bioregulation and Gerontology, North-Western Branch RAMS

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Introduction: Milestones of biogerontology development in Russia

The analysis of gerontological science in Russia has been given in recent works which also outlined

prospects for its development in the coming years (Anisimov 2001; Mikhailova et al. 2005). In this paper we will focused mainly on recent research obtained during 2005–2010 by Russian researchers permanently staying mainlty at the homeland. However, it is worthy to note several key events in the history of Russian gerontology. First of all, this is a book by I. Metschnikoff «Etudes sur la nature humaine: Essai philosophie optimiste» (1903), where he introduced the term «gerontology» and put the cornerstone of the scientific discipline in biology and physiology of aging. In the 1920s of the twentieth century the works of N.A. Belov, A.A. Bogdanov, S.A. Voronov, M.S. Milman, I.I. Schmalhausen not only evoked interest towards the investigation in the processes of aging per se, but also raised the question on the possible increase in the life span of animals and humans. The 1930–1940s are characterized by the origin of the first national gerontological schools in USSR—in Kiev and Kharkov (A.A. Bogomolets, A.V. Nagorny, I.N. Bulankin) and in Leningrad (Z.G. Frenkel, E. S. Bauer, V.G. Baranov). In 1938 in Kiev there took place the first scientific conference on aging. In 1957 in Leningrad on the initiative of Z.G. Frenkel there was organized the very first in this country City Scientific Society of Gerontologists and Geriatricians. The same year in Moscow there was organized the section of gerontology within Moscow Society of Nature Testers (MSNT). In 1958 there was established Research Institute of Gerontology of the USSR Academy of Medical Sciences in Kiev. In 1963 in Kiev there took place the first All-Union Conference (Congress) on Gerontology and Geriatrics. The Academic Council in Gerontology and Geriatrics of the USSR Academy of Medical Sciences alongside with section «Biological and Social Bases of Gerontology» of the Joint Research Council in Human Physiology of the USSR Academy of Sciences and Academy of Medical Sciences coordinated research work in all Union republics. A long-term All-Union comprehensive research programme in gerontology and geriatrics was elaborated in the period from 1981 to 1990. This period is characterized by active development of gerontology in the Ukraine and other regions of the USSR—in Leningrad, Moscow, Tbilissi, Kishinev, Minsk. Of great importance appeared to be workshops «Basic problems of aging» organized by N.M. Emanuel (1970–1984). The Group (Laboratory) of Mechanisms of Aging was organized by V.M. Dilman in 1973 at the Institute of Experimental Medicine in Leningrad.

Four All-Union Congresses were held in 1972, 1976, 1982 and 1988. In 1990 in Kiev the first issue of the All-Union (further Ukrainian) Journal "Problems of Aging and Longevity" saw the light. Major steps of Russian gerontology development up to middle 1980s of the last century are described in the monograph of Duplenko (1985).

Disintegration of the USSR resulted in the collapse of all former All-Union structures and actual closure of systematic studies in gerontology and geriatrics on the territory of the Russian Federation. Practically anew, we started looking for professionals and establishing research and practical institutions of this profile. The convocation of the Russian founding conference «Medical and social aspects in gerontology and geriatrics» organized by the St. Petersburg Scientific Gerontological society in March 1994 in St. Petersburg became a crucial moment in the modern history of Russian gerontology. Gerontological Society of the Russian Academy of Sciences (RAS) united leading scientists in gerontology and geriatrics around the country irrespective of their agency belonging. In 1996 the Gerontological Society joined European Regional Branch of International Association of Gerontology (IAG). Regular issuing of the information bulletin «Herald of the Gerontological Society of RAS» (www.gersociety.ru) started since 1996. In August 1997 at the 16th IAG World Congress in Adelaide (Australia) the Gerontological Society was accepted into the IAG and its representatives entered IAG Council. The same year the first issue of the journal «Advances in Gerontology» (St. Petersburg) and the 1st issue of the journal «Psychology of Maturity and Ageing» (Moscow) were published. The first Russian Congress of Gerontologists and Geriatrists was held in 1999 in Samara. In 2000 Saint Petersburg hosted the 2nd European Congress on Biogerontology with 300 participants from 33 countries. In June 2002 in Moscow there was held the 6th European Congress of Clinical Gerontology, and in October 2003, also in Moscow,—the 2nd Russian Congress of Gerontology and Geriatrics. The 6th European Congress of IAGG held on 5–7 July 2007 in St. Petersburg was an event of utmost importance for European and Russian gerontology. It gathered over 1500 participants from 70 countries of the world. The role of international

collaboration in development of the biogerontology in contemporary Russia was in detail describef elsewhere (Mikhailova et al. 2005).

On the initiative of the Gerontological Society a scientific specialty «Gerontology and Geriatrics—medical and biological sciences» has been introduced into the official list of specialties of the Russian Federation Ministry of Industry and Science in 2001, two dissertation councils were set up: at the St. Petersburg Institute of Bioregulation and Gerontology and Russian Research Institute of Gerontology at Moscow; first 200 thesis were defended on the new specialty. It is worth noting that numerous researchers from Ukraine, Belarus, Kazakhstan and Uzbekistan upheld their theses at the Dissertation Councils in Russia. The award and mutual recognition of scientific degrees in different countries will foster education and training of researchers and finally, progress of gerontological studies.

Chronology of most important events in the development of Russian biogerontology is given in the Table 1.

The Gerontological Society and development of biogerontology in Russia

The primary objectives of the Gerontological Society of the Russain Academy of Sciences consist in promoting the development of gerontology and related fields of physiology and biology; integrating research results with practice; establishing and maintaining contacts with scientific gerontological institutions of the CIS and other countries and with

Table 1 Chronology of Russian biogerontology development (1957–2010)

Year	Event
1957	Set up of the Leningrad Scientific Society of Gerontologists and Geriatricians. Organization of the Gerontological Section in the Moscow Society of Nature Testers (MSNT)
1958	Establishment of the Research Institute of Gerontology of the USSR Academy of Sciences (Kiev)
1963	1st All-Union Conference (Congress) of Gerontologists and Geriatricians
1970-84	Workshops «Fundamental problems of aging» (Moscow)
1973	Laboratory of Mechanisms of Aging at the Institute of Experimental Medicine (Leningrad)
1991	The 1st issue of the journal "Problems of aging and longevity" (Kiev)
1992	Foundation of the St. Petersburg Institute of Bioregulation and Gerontology
1994	Russian founding conference «Medical and social aspects in gerontology and geriatrics» (St. Petersburg); Organization of the Gerontological Society of the Russian Academy of Sciences (RAS);
1996	The 1st issue of the "Herald of Gerontological Society of the RAS" (St. Petersburg)
1997	The Gerontological Society of the RAS joined IAG
	The 1st issue of the journal "Advances in Gerontology" (St. Petersburg);
	The 1st issue of the journal "Psychology of Maturity and Aging" (Moscow)
1998	Organization of the Scientific council on gerontology and geriatrics of the Russian Academy of Medical Sciences and Russian Federation Ministry of Health
1999	1st Russian Congress of Gerontologists and Geriatrists (Samara)
2000	2nd European Congress on Biogerontology (St. Petersburg)
2001	Institution of a new scientific specialty 14.00.53—"Gerontology and Geriatrics"; Organization of two dissertation councils for upholding doctorate and candidate thesis in gerontology and geriatrics (Moscow, St. Petersburg)
2003	2nd Russian Congress of Gerontologists and Geriatricians (Moscow)
2007	The 6th European Congress of the IAGG (St. Petersburg)
2009	The first edition of a complex interdisciplinary programme of basic research "Science against aging"
2009	St. Petersburg Institute of Bioregulation and Gerontology is designated an IAGG Collaborating Centre
2010	United Nations Economic and Social Council (ECOSOC) granted a Special consultative status to the St. Petersburg Institute of Bioregulation and Gerontology

international non-governmental scientific organizations; organizing and convening meetings to exchange and discuss research and practical issues; assisting Society members in improving their professional skills and research activities; providing research and methodological assistance in teaching gerontology and geriatrics at higher schools and those for paramedical personnel; membership in international scientific associations and participating in the international meetings; fostering and distributing knowledge and recent scientific achievements in the field of Society's activity.

At the date of its foundation in 1994 the Gerontological Society consisted of seven regional branches. The participants of the Founding conference numbered 100 people. Today it embraces 45 branches with over 1500 members from more than 50 regions. Great attention in the Society is given to young researchers. In 1995 there was instituted the Award for young Russian scientists which is annually granted for the best research work in the field of gerontology and geriatrics. Since then about 20 young researchers became its laureates. Upon the recommendation of the Gerontological Society a few young researchers and practitioners participated in the International courses and schools in gerontology and geriatrics. International schools in gerontology and geriatrics organized by the Satellite Centre of the International Institute on Aging (INIA)—UN (Malta), constituted by the INIA, Gerontological Society of the Russian Academy of Sciences, Saint Petersburg Institute of Bioregulation and Gerontology and the City Geriatric Medical and Social Centre were held in 2002, 2004, 2007 and 2009 in St. Petersburg. Since 1994 there were held over 250 scientific conferences on different aspects of gerontology and geriatrics.

Basic research in biogerontology: impact of Russia

Recent years were exciting for increasing our understanding of ageing and its relationship to age-associated diseases, and developing promising strategies and candidates for pharmacological interventions into the ageing process (Blagosklonny et al. 2010). Some results of Russian researchers obtained during 2005–2010 have had rather a significant impact on ageing research.

DNA response and ageing

Genetic and biochemical studies have shown that PARP-1 and poly(ADP-ribosyl)ation play an important role in DNA repair, genomic stability, cell death, inflammation, telomere maintenance, and suppression of tumorigenesis, suggesting that the homeostasis of poly(ADP-ribosyl)ation and PARP-1 may also play an important role in ageing (Shram et al. 2006; Piskunova et al. 2007). Piskunova et al. (2008) found out that PARP-$1^{-/-}$ mice exhibited a reduced life span and a significant increase in population ageing rate. The analysis of noninvasive parameters, including body weight gain, body temperature, estrous function, behavioral, and a number of biochemical indices evidenced the acceleration of biological ageing in PARP-$1^{-/-}$ mice. The incidence of spontaneous tumors in both PARP-$1^{-/-}$ and PARP-$1^{+/+}$ groups is similar; however, PARP-$1^{-/-}$ mice developed malignant tumors at a significantly higher rate than PARP-$1^{+/+}$ mice (72% and 49%, respectively; $P < 0.05$). Moreover, spontaneous tumors appear sooner in PARP-$1^{-/-}$ mice as compared to the wild type group. These results demonstrate that inactivation of DNA repair gene PARP-1 in mice leads to acceleration of ageing, shortened life span and increased spontaneous carcinogenesis.

Genetics of ageing

Numerous publications extended knowledge on the role of genes in ageing and age-related pathology (Baranov and Baranova 2007; Glotov and Baranov 2007; Moskalev 2008). The analysis of survival among different Drosophila lines has revealed that recessive lethal mutation located in X-chromosome locus *6d1-7a2*, as compared to wild type strain, in heterozygote leads to ageing rate acceleration, median and maximal life span increase (Moskalev and Plyusnina 2007). Mutational analyses in model organisms have shown that genes affecting metabolism and stress resistance regulate life span, but the genes responsible for variation in longevity in natural populations are largely unidentified (De Luca et al. 2003; Magwire et al. 2010).

DNA–protein complex of cellular nucleus (chromatin) organizes into chromosomes only in case of cell division. In stationary state chromatin is found in two forms: euchromatin and heterochromatin.

Heterochromatin is usually localized in the nucleus periphery and contains generally inactive part of genome: genes blocked by repressor. Small peptides activate heterochromatin in the cell nuclei in senile patients and facilitate the «release» of genes suppressed as a result of heterochromatinization of chromosome euchromatin areas. These experimental results brought us to a conclusion that chromatin heterochromatinization is a reversible process which confirms a possibility of restoring protein synthesis, hence, organism functions (Khavinson et al. 2003). Reliable antimutagenic and reparative activity of thymus and pineal gland peptides have been confirmed by a reduction in the number of chromosome aberrations in the bone marrow cells and cornea epithelium cells in animals revealing accelerated ageing (Khavinson and Malinin 2005; Kossoy et al. 2003). It was established that administration of peptides Lys-Glu and Ala-Glu-Asp-Gly to transgenic mice caused a 2–3.6-fold suppression of HER-2/neu gene expression (human breast cancer) as compared to the control group. This suppression is accompanied by a reliable reduction of the tumor diameter (Anisimov et al. 2002a, b).

Imyanitov (2009) introduced a novel design for molecular epidemiological study, which relies on selection of highly demonstrative cases and controls. It is assumed that patients with clinical features of hereditary predisposition (e.g., cancer bilaterality, or young onset, or presence of family history, etc.) are more likely to accumulate at-risk alleles than randomly recruited cases. Furthermore, subjects with characteristics of cancer tolerance, e.g., elderly tumor-free smokers, may serve as a "supercontrol" for the rapid assessment of polymorphic candidates. The utility of the "comparison of extremes" design has already been exemplified in a series of reports. However, the use of elderly subjects for cancer case–control studies may possess a bias; for example, factors contributing to cancer predisposition may nevertheless be advantageous for the overall longevity, as they could compensate age-related decline of tissue maintenance and renewal. For example, there is some evidence for a dual role of the apoptosis-deficient Pro/Pro genotype of p53 gene, which may simultaneously increase both cancer risk and survival.

Gene polymorphism of catalase (*CAT, −262C/T*), glutathione peroxidase 1 (*GPX1, L198P*) and methionine sulfoxide reductase A (*MSRA, −402C/T*) were studied in 1534 samples of ethnic Tatars and it was found prevalence of combination of genotypes *CAT*C/*T-GPX1*L/*L* were significant for elderly and senile age (Pauk et al. 2008).

An atypical case of Werner syndrome has been described (Smirnova et al. 2008). It was shown that the DNA double-strand breaks repair after irradiation was significantly reduced in the cells of ataxia-telangiectasia patients as compared to the healthy donor's cells (Polubotko et al. (2009). A DNA damage response may occur in senescent cells even in the absence of detectable DNA damage (Pospelova et al. 2009).

Mitochondria, oxidative stress and ageing

Koltover (2009) presents a number of experimental data to show that in vivo antioxidants increase the system reliability, e.g. butylated hydroxytoluene can prevent production of O_2^- in mitochondria, whereas flavonoids can induce expression of antioxidant enzymes, superoxide dismutase (SOD) and catalase. The study of the effect of psycho-emotional stress in young (6–8 years) and old (20–26 years) rhesus monkey demonstrated that age-related alteration in SOD and glutathione reductase stress responsiveness lead to activation of peroxide oxidation of lipids that may be considered as an important factor of ageing (Goncharova et al. 2006, 2008).

Pharmacological intervention in ageing

The ultimate goal of biomedical research is the development of therapeutic drugs. Method of evaluating the effect of pharmaceuticals on ageing and life span in mice developed at Petrov Research Institute of Oncology was included in the manual "Biological Ageing: Methods and Protocols" published in the USA (Anisimov et al. 2007). Plastoquinone, a very effective electron carrier and antioxidant of chloroplasts, was conjugated with decyltriphenylphosphonium to obtain a cation easily penetrating through membranes. This cation, called SkQ1, was shown to be specifically targeted to mitochondria by means of electrophoresis in the electric field formed by mitochondrial respiratory chain. The same chain is shown to regenerate reduced $SkQ1H_2$ from its oxidized form that appears as a result of the antioxidant activity of $SkQ1H_2$. It is shown that $SkQ1H_2$ prevents oxidation

of cardiolipin, a mitochondrial phospholipid that is especially sensitive to attack by reactive oxygen species (ROS). In cell cultures, SkQ1 and its analog plastoquinonyl decylrhodamine 19 (SkQR1) are shown to arrest H_2O_2-induced apoptosis. When tested in vivo, SkQs (i) prolong the lifespan of fungi, crustaceans, insects, fish, and mice, (ii) suppress appearance of a large group of traits typical for age-related pathologies (cataract, retinopathies, achromotrichia, osteoporosis, lordokyphosis, decline of immune system, myeloid shift of blood cells, activation of apoptosis, induction of β-galactosidase, phosphorylation of H2AX histones, etc.) and (iii) lower tissue damage and save the lives of young animals after treatments resulting in kidney ischemia, rhabdomyolysis, heart attack, arhythmia, and stroke. It is suggested that the SkQs prevent increase in mitochondrial ROS level, which seems to induce age-related mitochondria-mediated apoptosis, an obligatory step of execution of programs responsible for both senescence and fast "biochemical suicide" of an organism after a severe metabolic crisis (Skulachev et al. 2009). It was demonsrated that SkQ1 inhibits age-dependent involution of the thymus in normal and senescence-prone OXYS rats (Obukhova et al. 2009).

It was revealed that addition of tetrapeptide Ala-Glu-Asp-Gly to the cultural medium of human lung fibroblasts induces telomerase gene expression and contributes to a 2.4-fold lengthening of telomeres. Activation of gene expression is accompanied by a growing number of cellular divisions (by 42.5%) (Khavinson et al. 2004a, b). This fact fully correlates with earlier stated maximum increase of animal life span (42.3%) after administration of this peptide (Anisimov et al. 2001).

Peptidergic regulation of ageing

The results of long-term investigations in the mechanisms of ageing and a role of peptide bioregulators in prevention of age-related pathology have been summarized (Khavinson 2002; Khavinson and Malinin 2005; Anisimov and Khavinson 2003, 2005, 2010). A number of small peptides have been isolated from different organs and tissues and their analogues (di-, tri-, tetrapeptides) were synthesized from the amino acids. In a number studies it was shown that long-term treatment with some peptide preparations increased mean life span by 20–40%, slow down the age-related changes in the biomarkers of ageing and suppressed development of spontaneous and induced by chemical or radiation carcinogens tumorigenesis in rodents. Possible mechanisms of the biological effects of small peptides were studied. It was revealed that small peptides (di-, tri- and tetrapeptides) are capable of complementary interaction with the DNA specific binding site on the promoter segment of genes, inducing disjoining of double helix strands and RNA polymerase activation. Discovery of the phenomenon of peptide activation of gene transcription points out the natural mechanism of organism to maintain physiologic functions, which is based on the complementary interaction of the DNA and regulatory peptides. This process is fundamental for the development and functioning of the living substance, while ageing is an evolutionary determined biologic process of age-related changes in gene structure and expression (Khavinson et al. 2005, 2008; Anisimov and Khavinson 2010).

Addition of small peptides to ectoderm polypotent cells in the same experimental model led to the onset of various tissues. These experiments showed that peptides are able to induce cell differentiation in regard to the structure of the substance added. The analysis of results obtained gives every ground to conclude that it is quite possible to induce deliberately differentiation of polypotent cells and to use biological reserve of various organs and tissues of the organism contributing to prolongation of life up to species limit (Khavinson 2002; Khavinson et al. 2002).

The effect of di- and tetrapeptides Lys-Glu, Glu-Trp, Ala-Glu-Asp-Gly, Ala-Glu-Asp-Pro on the expression of 15,247 murine heart and brain genes before and after peptides administration was studied with the employment of DNA-microarray technology. In this experiment, there were used clones from the library of the National Institute on Aging, USA. This experiment provided unique data on alteration in the expression of different genes under the effect of peptide preparations. An important conclusion driven from the experiment was that every peptide specifically regulates particular genes. Results of this experiment testify to the existing mechanism of peptide regulation of gene activity. It was also registered that dipeptide Lys-Glu, showing immunomodulating activity, regulates gene interleukin-2

expression in blood lymphocytes (Anisimov et al. 2002a, b, 2004; Khavinson and Malinin 2005).

Restoration of the melatonin level in old monkeys (20–26 years old) up to normal (typical for young animals 6–8 years old) following administration of the peptide preparation was among the most significant achievements. The same old monkeys revealed a restoration to normal indices of a daily rhythm of secretion of the main hormone of adrenal gland—cortisol. Administration of the peptide or pineal preparation to old animals led also to restoration of disturbed with ageing glucose tolerance (Goncharova et al. 2005; Khavinson et al. 2001).

It was shown that the pineal peptides enhance the antioxidant defence system, which can contribute to their geroprotective properties (Kozina et al. 2007).

Carnosine (β-alanine–L-histidine) is a neuroprotective dipeptide which demonstrates a number of useful features, including brain stimulation and muscle microcirulation and a rejuvenating effect on cultured cells (Boldyrev et al. 2010). It was shown that its activity is based on its antioxidant and antiglycating action that in addition to heavy metal chelation and pH-buffering ability, makes carnosine an essential factor for prevention of neurodegeneration and senescence. Carnosine at physiological concentration might remarkably reduce the rate of telomere shortening in the lens cells subjected to oxidative stress (Babizhaev and Yegorov 2010).

Calorie restriction mimetics in ageing and cancer

Ageing is associated with obesity and cancer. Calorie restriction both slows down ageing and delays cancer. Evidence emerges that the nutrient-sensing mTOR pathway is involved in cellular and organismal ageing. It was shown that the mTOR inhibitor rapamycin prevents age-related weight gain, decreases rate of ageing, increases life span and decreases carcinogenesis in transgenic HER-2/neu cancer-prone mice. Rapamycin dramatically delayed tumor onset, decreased the number of tumors per animal and tumor size (Anisimov et al. 2010a). The results obtained suggest that, by slowing down organismal ageing, rapamycin delays cancer. The phosphoinositide 3-kinase (PI3K) and TOR-kinase cascades are affected in some long-lived mutants of different animals, such as nematodes and mice. The purpose of this study was to investigate the geroprotector efficiency of the inhibitors of enzymes that are known to be affected in long-lived mutants. Experimental animals were exposed to low dozes of LY-294002 (5 μM), wortmannin (0.5 μM), and rapamycin (0.5 μM) separately during their lifetimes. The specific PI3K inhibitors (LY-294002 and wortmannin) and the TOR-kinase inhibitor rapamycin slightly increased the median and maximal lifespan of the fruit fly, Drosophila melanogaster (Moskalev and Shaposhnikov 2010).

In early 1970s, Professor Vladimir Dilman originally developed the idea that antidiabetic biguanides may be promising as geroprotectors and anticancer drugs (Dilman 1971; Dilman and Anisimov 1980). In 2005 it was shown that chronic treatment of female transgenic *HER-2/neu* mice with metformin significantly reduced the incidence and size of mammary adenocarcinomas (MAC) and increased the mean latency of the tumors (Anisimov et al. 2005). Than we demonstrated that the chronic treatment of female outbreed Swiss-derived SHR mice slowed down the age-related switch-off of estrous function, increased mean life span by 37.8%, mean life span of last 10% survivors by 20.8%, and maximum life span by 10.3% in comparison with control mice (Anisimov et al. 2008b). In 2010, it was shown that metformin in smaller doses increased mean life span by 8% and MAC latency by 13.2% in HER-2/neu mice and inhibited the growth of transplantable HER-2 MAC in male FVB/N mice by 46% (Anisimov et al. 2010a, b). Administration of metformin suppressed benzo(a)-pyrene (BP)-induced skin, soft tissues and cervicovaginal tumorigenesis in mice (Deriabina et al. 2010a, b).

Epidemiological studies have confirmed that metformin, but not other anti-diabetic drugs, significantly reduces cancer incidence and improves cancer patients' survival in type 2 diabetes (Berstein 2005; Evans et al. 2005; Martin-Castillo et al. 2010). As it was noted by Martin-Castillo et al. (2010), at present pioneer works by Dilman & Anisimov at the Petrov Rsearch Institute of Oncology (St. Petersburg, Russia) is rapidly evolving due to ever-growing preclinical studies using human tumor-derived cultured cancer cells and animal models. Metformin exterts anti-tumoral effects by activating AMPK which, in turn, suppresses activity of the mammalian Target Of Rapamycin (mTOR) and lastly decreases activity of mTOR (Alimova et al. 2009). It was observed that metformin has dual

effects—insulin reduction and mTOR—a master integrator of cell growth and division in response to energy state, nutrient status, and growth factor stimulation,—along with the modulation of several other targets (e.g., p53, p21, Cyclin D, Src, etc.) (Liu et al. 2009). There are at least seven open studies evaluating the efficacy and safety of treating cancer patients with metformin (Martin-Castillo et al. 2010).

Olovnikov (2007) proposed that a primary cause of ageing is a process of shortening of hypothetical perichromosomal DNA structures termed chronomeres. The life long clock is regulated by the shortening of chronomere DNA in postmitotic neurons of the hypothalamus. Shortening of these DNA sequences occurs in humans on a monthly basis through a lunasensory system and is controlled by release of growth hormone discharged from the anterior pituitary directly into the hypothalamus via local blood vessels. In adults, this process is under control of the pineal gland. It was also suggested that a calorie restricted diet retards chronomere shortening due to a local deficit of growth hormone in the surroundings of hypothalamus cells, thus slowing the lifelong clock and delaying ageing. Calorie restriction increases lifespan by preserving mitochondrial and other organismal functions owing to the decreased chronomere shortening.

Circadian clock and ageing

The alternation of the day and night circadian cycle is a most important regulator of a wide variety of physiological rhythms in living organisms, including humans. Due to the appearance of electricity and artificial light about 100 years ago the pattern and duration of human exposure to light has changed dramatically, thus light-at-night has become an increasing and essential part of modern lifestyle. Light exposure at night seems to be associated with a number of both serious behavioral and health problems, including excess of body mass index, cardiovascular diseases, diabetes and cancer (Anisimov 2006b; Stevens 2009). The effect of various light/dark regimens on the survival, life span and tumorigenesis was evaluated in rats kept at various light/dark regimens: standard 12:12 light/dark (LD); natural lighting of the North-West of Russia (NL); constant light (LL), and constant darkness (DD) since the age of 25 days until natural death (Vinogradova et al. 2009). It was found that exposure to NL and LL regimens accelerated development of metabolic syndrome and spontaneous tumorigenesis, shortened life span both in male and female rats as compared to the standard LD regimen. Thus, the circadian disruption induced by light-at-night accelerates ageing and promotes tumorigenesis in rats. This observation supports the conclusion of the International Agency Research on Cancer that shift-work that involves circadian disruption is probably carcinogenic to humans (Straif et al. 2007). It is worthy of note that melatonin alleviated the effects of circadian disruption, prevent premature ageing and tumorigenesis (Anisimov et al. 2006).

Cancer and ageing

A significant attention has been paid to a problem of relationship between cancer and ageing. Carcinogenesis is a multistage process: neoplastic transformation implies the engagement of a cell through sequential stages, and different agents may affect the transition between continuous stages. Multistage carcinogenesis is accompanied by disturbances in tissue homeostasis and perturbations in nervous, hormonal, and metabolic factors which may affect antitumor resistance. The development of these changes depends on the susceptibility of various systems to a carcinogen and on its dose. Changes in the microenvironment may condition key carcinogenic events and determine the duration of each carcinogenic stage, and sometimes they may even reverse the process of carcinogenesis. These microenvironmental changes influence the proliferation rate of transformed cells together, the total duration of carcinogenesis and, consequently, the latent period of tumor development. Ageing may increase or decrease the susceptibility of various tissues to initiation of carcinogenesis and usually facilitates promotion and progression of carcinogenesis. Ageing may predispose to cancer by two mechanisms: tissue accumulation of cells in late stages of carcinogenesis and alterations in internal homeostasis, in particular, alterations in immune and endocrine system. Ageing is associated with a number of events at molecular, cellular and physiological levels that influence carcinogenesis and subsequent cancer growth (Anisimov 2005, 2007, 2009; Anisimov et al. 2009; Schwartzburd 2008).

Evolution and ageing

The evolution aspects of ageing are in the focus of interest of Russian gerontologists (Makrushin 2008; Skulachev 2009; Moskalev 2010). Popov (2008) discussed the evidences on the existence of "species senescence" phenomenon. He believes that species transform inevitably with the changes of generations even if they are already well adapted to their environment.

Demography of ageing

Safarova et al. (2005) demonstrated a significant regional differentiation of ageing characteristics (e.g. the proportion of population aged 60 and over, ageing index, old-age dependency ratio) in the Russian Federation. The UN Population Prospects (The 2004 Revision) and probabilistic projections for Russia and Ukraine up to year 2050 were analyzed (Pirozhkov et al. 2007). Some demographic indices of the ageing and longevity in Yakutia were evaluated (Tatarinova and Nikitin 2008). Tatarinova et al. (2008) presented results of the examination of a 117-years long-liver person in Yakutia. Mamaev and Tsarin (2007) described historical dynamics of age-related mortality of men and women in 12 Western countries.

Biological age and biomarkers of ageing

Bashkireva and Khavinson (2007) studied biological age, ageing rate, occupational performance in automobile drivers. It was shown that premature ageing of physiological parameters in drivers is proved to be only "risk indicators", whereas prolonged length of service in driving is a real risk factor acceleration ageing process. Accelerated development of atherosclerosis and of ageing of immune system and of the veterans of special risk subdivisions participated in nuclear weapon tests was described by Alishev et al. (2007, 2010). It was shown that the influence of fibrogenic aerosols leads to the increase in biological age of patients with the dust diseases of lungs (Kosarev et al. 2009).

Gerontology in silico

One of most perspective directions of research including analyses of demographic, molecular, cellular and physiological mechanisms of ageing, the role of the DNA damage and repair, cell proliferation and apoptosis, is an application of mathematical modeling in experimental gerontology including modeling ageing and longevity in laboratory animals. Russian researchers are leaders in this growing field (Demyanov 2005; Marchuk et al. 2007; Yashin et al. 2007; Mikhalski and Novoseltsev 2005; Golubev 2009a, b).

Prospects of Russian gerontology development

Despite growing interest to research in gerontology in Russia during recent 15 years, creation of infrastructure (establishment of profile research institutions, issue of new specialized journals, introduction of a new scientific speciality «Gerontology and Geriatrics», etc.) and a number of obvious scientific achievements of Russian gerontologists, it should be noted that there is definite lack of governmental support, financial, in particular, especially in regard to basic research. It dooms national gerontology to backlog in development and inhibits solution of urgent problems the country faces. Demographic situation in Russia (decreased birth rate, increased proportion of old people in the structure of population, especially in big cities, such as Moscow, Saint Petersburg, Ekaterinburg, Novosibirsk and other, unprecedented decrease of expected life span, decreased number of people of the working age and their premature ageing) and unfavorable demographic prognosis for the coming decades (Pirozhkov et al. 2007), put forward not only the issue of health in Russia, but its economic and political safety.

Table 2 contains a detailed list of priorities in up-to-date fundamental gerontology with reference to leading Russian institutions engaged in the studies at a high professional level providing publication of the results obtained in the reputable peer-reviewed national and international journals.

The contribution of Russian science into major priorities of the world biogerontology is manifested by few groups of researchers conducting up-to-date studies. The research made by them in respect to above directions produce considerable and sometimes decisive impact on the solution of particular scientific tasks, which is confirmed by the level of publications, and their lecturing as invited speakers at the top International forums on gerontology, where they

Table 2 Priorities in current biogerontology: participation of Russia

Research directions	Leading institutions in Russia, City	Selected references
Demography of aging	SPb Economy and Mathematics Institute, RAS;	Safarova et al. (2005)
	Institute of Therapy, RAMS (Novosibirsk);	Tatarinova and Nikitin (2008)
	IBCP, RAS (Moscow)	Mamaev and Tsarin (2007)
Genetics of aging and longevity	RIOG, RAMS (St. Petersburg);	Glotov and Baranov (2007)
	Institute of Biochemisty and Genetics, RAS (Ufa)	Pauk et al. (2008)
	Institute of Biology, RAS (Syktyvkar)	Moskalev (2008)
	Institute of Molecular Genetics, RAS (Moscow)	Rybina and Pasyukova (2010)
Progeria	Institute of Cytology, RAS (St. Petersburg)	Smirnova et al. (2008)
Cell aging, telomere	Institute of Molecular Biology, RAS (Moscow)	Moldaver and Yegorov (2009)
	Institute of Cytology, RAS (St. Petersburg)	Khavinson and Malinin (2005)
	SPb IBG RAMS (St. Petersburg)	
Evolution aspects of aging	Institute of Biology on Inner Water, RAS (Borok);	Makrushin (2008)
	Institute of Zoology, RAS (St. Petersburg)	Popov (2008)
Mitochondria, oxidative stress	IPCB, Lomonosov Moscow State University	Skulachev (2009)
	IPCP, RAS (Chernogolovka)	Koltover (2009)
	IGC, RAS (Novosibirsk)	Shnitnikova et al. (2009)
	RIOG, RAMS (St. Petersburg);	Kozina et al. (2007)
	Astrakhan State University	Abatnina et al. (2005)
Pineal gland and aging	SPb IBG RAMS (St. Petersburg);	Khavinson (2002)
	Petrov Research Institute of Oncology (St. Petersburg);	Anisimov et al. (2002a, b, 2003)
		Anisimov and Khavinson (2005, 2010)
	Institute of Medical Primatology, RAMS (Sochi)	Goncharova et al. (2008)
	Petrozavodsk State University	Vinogradova et al. (2009)
Peptide regulation of aging	SPb IBG, RAMS (St. Petersburg)	Khavinson (2002)
	Petrov Research Institute of Oncology (St. Petersburg);	Khavinson and Malinin (2005)
		Anisimov and Khavinson (2010)
	Lomonosov Moscow State University	Boldyrev et al. (2010)
Cancer and aging	Petrov Research Institute of Oncology (St. Petersburg)	Anisimov (2006a, c, 2007, 2009)
Theories of aging	Lomonosov Moscow State University;	Severin and Skulachev (2009)
	IBCP, RAS (Moscow);	Olovnikov (2007)
	ICP, RAS (Moscow);	Gladyshev (2005, 2006)
	RIEM, RAMS (St. Petersburg)	Golubev (2009a, b)
Mathematic models of aging	Institute of Control Sciences, RAS (Moscow);	Mikhalski and Novoseltsev (2005);
	Institute of Numerical Mathematics, RAS (Moscow);	Marchuk et al. 2007
	RIEM, RAMS (St. Petersburg)	Golubev (2009a)
	St. Petersburg State University;	Demyanov (2005)
	Ul'yanovsk State University	Butov et al. (2002)
Geroprotectors	SPb IBG RAMS (St. Petersburg);	Khavinson (2002);
	Petrov Research Institute of Oncology (St. Petersburg);	Khavinson and Malinin (2005);
		Anisimov and Khavinson (2003, 2005, 2010);
		Anisimov (2008);
		Anisimov et al. (2005, 2007, 2010a, b);
	IPCB (Moscow);	Skulachev et al. (2009)
Biomarkers of aging	SPb IBG RAMS (St. Petersburg);	Bashkireva et al. (2009)
	SMC-CVSRS (St. Petersburg)	Alishev et al. (2007, 2010)

organize symposia and topical sessions and often are awarded with international grants.

The bulk of investigation carried out by Russian researchers according to certain directions is quite substantial, but unfortunately their publications are rather rare in leading international journals. Many of them, do not meet the requirements of such journals due to weak methodological basis, thus they cannot contribute to the development of the issue they dwell on. At the same time some of them could've undoubtedly shown up-to-date professional level should their research be supported and their laboratories up-graded. It is worthy of note, that there are growing number of publications of results of joint teams, included Russian and western researhcers. Russian and International research foundations and companies exert financial assistance to some Russian researchers supporting especially those investigations which promise practical application of the results obtained. Numerous experimental data are obtained due to bilateral collaboration with western institutions on the finance-free basis.

The dynamics of publications of Russian authors in gerontology and geriatrics in the period from 1994 to 2006 was presented in the bibliography of publications of Russian researchers, 1994–2006 (Kudryavtseva 2007a). Over 13% of them are published in International peer-reviewed journals (Kudryavtseva 2007b).

In general, it may be stated that gerontology has not yet entered the range of sciences, supported by the government on a constant basis.

Historically, research schools in Russian gerontology got shape within the framework of other disciplines. However, today we can talk about the existence, rather formation of research schools, where gerontology studies occupy a substantial proportion. It should be emphasized that formation of steady research schools in gerontology is a marker of progress in this discipline and its growing topicality, which in its turn, reflects global changes in demographic situation and society demands in general. We believe that the development of gerontology would be more effective under governmental support. Enrollment of gerontology into the classifier of research directions sponsored by the Russian Foundation for Basic Research could play its positive role. Of utmost importance seems the "Programme for prevention of age-related pathology and accelerated ageing, reduction of premature mortality due to biological reasons and extension of healthy period of life for the population of Russia" developed on the basis of the latest achievements of Russian researchers on the initiative of the St. Petersburg Institute of Bioregulation and Gerontology (Anisimov et al. 2008a; Khavinson and Mikhailova 2007). On the initiative of the non-government organization Russian Foundation for the support of scientific research "Science for Life Extension", a complex interdisciplinary programme for fundamental research "Science against ageing" was prepared. Both programmes were presented at the 19th IAGG World Congress of Gerontology and Geriatrics, Paris, 2009 (Batin et al. 2009).

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