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Time for a New Paradigm in Oncology? Viewpoint of the Radiobiologist

Aleksey N. Shoutko

Department of Transplantation and Cells Technologies, Russian Research Center of Radiology and Surgical Technologies Named after A. M. Granov, Saint-Petersburg, Russia
Email: shoutko@inbox.ru

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Abstract

The current immunooncology artificially ignores the connection with lymphopoiesis, though is only its derivative. Hematopoietic stem cells (HSC) provide physiological regeneration of biomass of the host, fetus, and malignant tumors, as well, as the cells' reparation after sub-lethally injuring in any tissues and their renewal. HSC, especially of lymphoid lineage, are the most vulnerable of those, which are responsible for viability of organism. Natural and artificial deficits of HSC determine aging, multi-organs syndromes and death of the host, because their current proliferative resource (CPR) is individually limited at birth, and is spending irreversibly during wounds' healing, pregnancy, tumor growth, and on. CPR, being an integral value of the number of stem cells along the length of their telomeres, is a "shagreen skin", for which the tumor competes with normal tissues as a quasi-embryonic favorite and winner, especially in the final period of a shortening the life. The primary approach to cancer treatment must prioritize the preservation of CPR remnants, rather than their destruction, in order to temporarily halt the malignant process. The re-targeting of HSC from tumors in favor of normal tissues is the immediate objective of competitive therapy, which allows for preserving the rest of the CPR host's resources, especially in patients with advanced cancer. However, the contradictory and insignificant practically, the dogma of antitumor cellular immunity continues to dominate and hinder progress in oncology.

Keywords

Lymphopoiesis, Proliferating Resource, Morphogenesis, Cancer-Fetus, Reparation-Regeneration, Competitive Therapy

1. Introduction

Correct analysis of the nature of malignant growth is impossible without the

consideration of general principles of the creation and renewal of biomass in the body. Instead of this, the dominant doctrine of immune-oncology implies the axiomatic formation of new antigens, which are alien to the host. It justifies the dogma of natural protection and fighting of the host against malignancy. All circulating white blood cells are assumed to a programmed to antitumor defense ultimately. The stages of cell differentiation in lymphopoiesis have been ignored, the immature cells are discussed only in terms of their supposed functional maturity, neglecting a natural process of cells' aging [1].

During 65 years of adaptation to the clinical results, cellular immunooncology became a very sophisticated branch of science, due to manifold ad hoc. To explain low practical justification [2] [3] [4], many reasons were involved, like a "suppression", "deception" of immunity by a tumor, down-regulation of tumor antigen presentations, an expression of molecules either to induce apoptosis of T lymphocytes, or to inhibit cytotoxic T lymphocytes, an expression of molecules for self-resisting to cytotoxic T-cells, a block of expression of molecules essential for co-stimulation of T cells, expression or overexpression of antiapoptotic molecules, like protein PD-L1 on the surface of tumor cells for resistance to effector mechanisms of NK and cytotoxic CD8+ T cell, regulatory T cells (Treg) with pro- and antitumor properties [5], which discovered even among cytotoxic CD8+ cells [6], and on.

Models of parameters inhibiting cancer immunity, and parameters promoting cancer immunity include 26 nodes and 107 interaction links [7], dissipating the attention to the actual mechanism and disorienting a search for effective approaches to treatment. Many modern authors continue to move away from the key processes at the level of the organism, exaggerating the role of molecular mechanisms that are nothing more than only subordinated ones [8]. They come to a conclusion about the existence of therapeutic enhancing antitumor immunity without consideration of elementary data like given below. Meanwhile, a rejection of malignant tissue remains a pipe dream of oncologists, whereas the retention of an allogenic graft and avoiding of its easiest natural rejection is an insoluble problem of a transplantologists, which both use one theory of cells immunity. The modern strategy of immunotherapy demands to reduce of regulatory T cells-"suppressors" in cases of cancer, but extends them in case of allograft [9]. It is not clear, why such opposite immune reactions are expected, if both malignant tissue and allograft, in the case being non-self, have to provoke a uniform anti-allogeneic response. It is not clear also, why the practice of therapy in both of the cases leads to uniform lymphocytopenia. Similarly, why the age-related decline in immunity associated with decreased survival of recipients of the liver allograft [10], but followed by improvement of mortality, incidence and prevalence of malignancy among old patients [11]. The favorite paths of the tumor cell's dissemination, namely blood, and lymph nodes, are the very location of supposed "protective" cells. The modern anti-angiogenic therapy [12] [13] prevents circulating lymphocytes from interacting with tumors. The idea of non-selective cytotoxic therapy as the stimulator of immune defense against tu-

mors dominates despite the main antineoplastic agents are carcinogenic, toxic, mutagenic, clastogenic, and teratogenic [14], and treated cancer survivors have an increasing risk of developing new malignancies by 14% compared with the general population [15]. The idea of a tumor's deception of immune protection is popular, in spite of the lowest limits of lymphocytopenia permitted at cancer therapy [16], are comparable with such for survivors after the nuclear bombing [17]. The last trend from "enhancement immunotherapy" (pushing the immune system to the supraphysiological level) to "normalization immunotherapy" (a "deceiving" the tumor, which has already deceived the immune system) [18] shows, in fact, an endless attempt to save the dogma of cancer immunogenicity. However, as far as the humoral immunity is clear, the cellular immunity remains so vague.

The aim of this review is to consider the processes, which are not in the view of immunooncologists. The considered data does not confirm the present total priority of the immune mechanisms in the theory and practice of modern oncology but confesses the collaboration between the host and malignant tissue as a quasi-embryonic part of the body [19]. The proposed conception solves the main controversies noted above, and is quite applicable to other pathologies, along with malignancy.

2. Hematopoiesis and Life Span Limitation

2.1. Bone Marrow

Classic radiobiology has established that among systems, responsible for saving of viability of the host itself, the hematopoietic one is the most injurable, and therefore limits a life span. Acute whole-body irradiation (WBI) provokes "hematopoietic" type of death during 1 - 2 months. Irreversible, not-recovered loss of hematopoietic stem cells (HSC) followed by "gastrointestinal" death in 3 - 6 days, due to the lack of natural morphogenic cells-migrant from bone marrow (BM), which provide regeneration of enterocytes in crypts, and thus, the integrity of mucosa lining. The rapid "gastrointestinal" death is indirect because gastrointestinal epithelial cells are more radioresistant than the lymphoid migrants. It has been proved by classic experiments with parabiotic animals, and by partial shielding of BM, as a source of HSC. The shielding from irradiation saves of HSC migrants with the property of endothelial progenitors (EPC) [20] [21] [22] [23] [24]. The source of HSC in tissues might be ubiquitous throughout the body. Very small (<2 microns) totipotent stem cells transient into pluripotent CD10, TdT (terminal deoxynucleotidyl transferase) cells for common lymphoid progenitors. Their level in blood changes from 2×10^{11} per l to 3×10^{10} per l [25] [26].

2.2. Aging

Surprisingly, natural myelosuppression starts right after birth and lasts during the entire life (**Figure 1**). The active (red) BM in humans is reduced during the first 40 years from 100 to 27% - 30% [27].

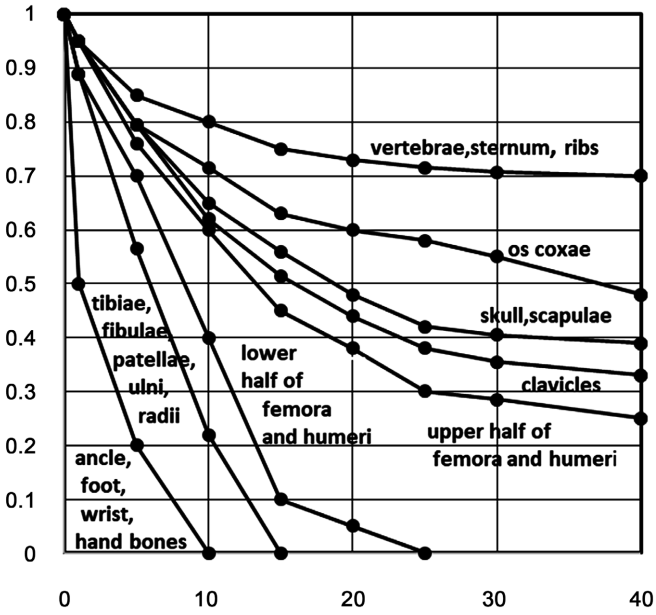

Figure 1. Natural involution of red bone marrow in the human body by age.

The CD34 HSC spends continuously during the life, colonizing the thymus and promoting repair-regeneration of BM and non-hematopoietic tissues as diverse as gastrointestinal epithelium, liver, heart, muscles, lungs, kidneys, skin, brain [28]. Moreover, the self-repopulation's capacity of each HSC decreases steadily, especially during the last third-quarter of life [29].

2.3. Thymus

The same natural involution is going by age in thymus, as the organ colonized by HSC from BM [30]. Among healthy people 25 - 75 years old, 22% and 97% have complete fatty replacement of the gland (**Figure 2**). From 52% to 3% of people have predominantly fatty attenuation (Score 1), from 18 to 0.5% have half fatty and half soft-tissue attenuation (Score 2), and only 8-0.1% have solid thymic gland with predominantly soft-tissue attenuation (Score 3, **Figure 2**).

Complete fatty replacement of thymus is coming for 80% of the old ≤ 39 years and for 97% of ≥ 70-year-old healthy humans. The irreversible and speedy involution of thymus in adults up to death does not much to generally accepted function of T-lymphocytes, but rather indicates their involvement in the renewal of the somatic sphere of the body during its aging, like the BM does. The cells of thymus relate to the increase and decrease of biomass during the development of organism. It follows obviously from the analysis of short postnatal period. During 1.2 - 1.3 months of life, the wet weight of thymus (TWW) increases 4-fold, and average mass of the body (MB), heart, lung, kidney, liver, spleen, pancreas, brain increase 2.34 ± 0.35-fold also [33]. A TWW during children's growth spurt (from 2.5 to 13 years old), continues to increase 1.4-fold (from 25 to 36 g), in parallel with 2,1-fold increasing the average rate of MB, with rate (MBR) from +2.3 kg per year to +5 kg per year) (**Figure 3**). Later, during 13 - 19.5 years old, the both

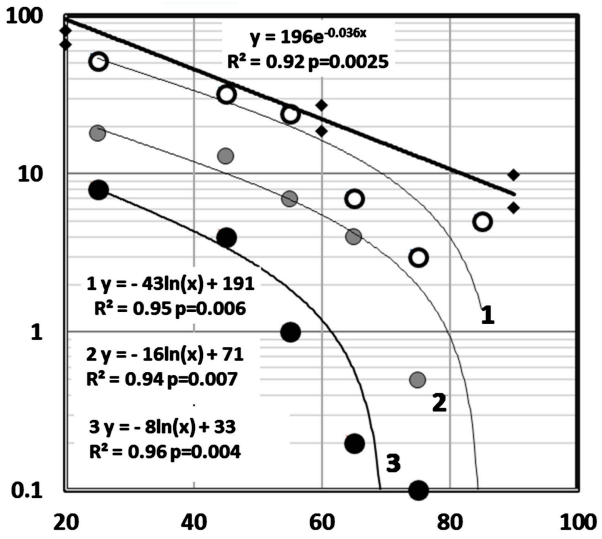

Figure 2. Natural involution of thymus and base metabolic rate during aging of adults. Abscissa: age, years. Ordinate: percentage of adult people with different levels of fatty degeneration in thymus (circles) and kilocalories per year for postnatal base metabolic rate of people (rhombuses). 1 (white)-predominantly fatty thymus; 2 (gray)-approximately one-half fatty and one-half soft-tissue attenuated thymus; 3 (black)- predominantly soft-tissue attenuated thymus [31]. Natural decellularization of both BM and thymus organs coincides with postnatal decreasing of the base metabolic rate (BMR, rhombuses; original data extracted and calculated from [32]).

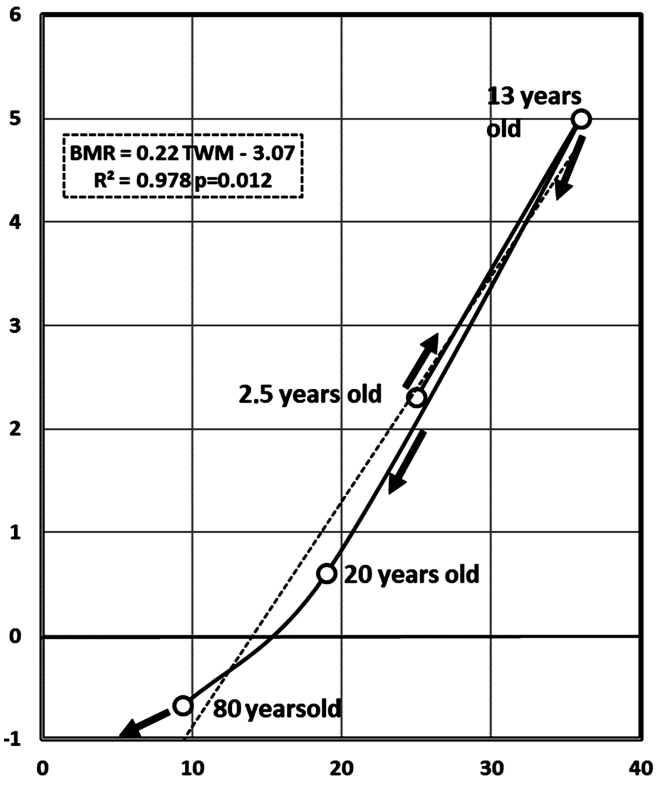

Figure 3. The dependence of the rate of mass of a body (MBR) from wet weight of human thymus (TWW) by age. Abscissa: TWW, g. Ordinate: MBR, kg per year. Dotted line: linear approximation of data.

TWW and MBR decrease 1.9-fold (from 36 to 18.7 g) and 8.3-fold (from 5 to 0.6 kg per year). To 20 years old, the thymus loses a half of its maximal mass, and continues to loss it up to 80 age from 19.5 to 9.4 g in parallel with decreasing of MBR from +0.6 to −0.68 g per year [34] [35].

The loss of fat-free body mass of aging adults, in parallel, is accompanied by the moderate loss of total T cells (69% to 61%) in blood, faster loss of naïve CD45RA + CCR7 + post-thymic cells (from 27% to15%), and fastest loss of stem CD34, TdT cells (from 0.25% to 0%). The stem CD34, TdT cells of teenagers dwell in cortex of thymus, which mass dominates over the medulla around 4 times. The involution of the cortex by age proceeds at a rate approximately two and a half times faster than that of the medulla. As a result, the thymus is the main source of lymphoid stem cells LSC (CD34, TdT, CD90, CD117) in blood during only the first half of life, but BM dominates during the second half [36].

Neither physiological involvement of Treg in the health of normal tissues, nor their natural cells aging at the telomeres' level [37], nor coexpression of T reg markers CD25 [38], CD31 [39], PD-L1 [40], VEGFR-2 [41] with markers of hematopoietic stem cells (HSC) CD133, CD34, CD90, CD117, CD127 [42] [43] [44] [45], nor kinetic transition of lymphopoiesis into abnormal (symmetric) regime with turbulent (periodic) production of innate lymphocytes [46]-[52], nor the nature of apoptosis as a holocrine type of secretion [53], nor a dependence of Treg number from the lymphopenia's level [54] [55] are not the points of polemical discussion in immune-oncology. Actually, the increased proportion of immature cells, in particular, "regulatory" lymphocytes (Treg) in cancer patients with lymphopenia is the first sign of functional overloading of lymphopoiesis, which is non-homeostatic, symmetric one. Their increasing manifests an inevitable failure of the natural level of stem cells' number and limitation of their self-reproduction by shortening of telomeres. The event of apoptosis-programmed cell death has been considered in relation to malignant cells mostly, though it is intrinsic for young lymphocytes and named in cell physiology as a secretion of the holocrine type, which promotes the proliferation of surrounding cells [53]. Ignoring this, oncoimmunlogists consider innate T reg cells with stem markers, as special members of immunity, which show sometimes an annoying pro-tumor activity [56].

3. Functional Resource of Stem Cells

3.1. Number in Circulation

The sign of specific T-cells maturation (sjTRECs-excision circles of extrachromosomal DNA) in most recent naive T-cell emigrants from the thymus decreases dramatically around 1000-folds from 20 to 60 age [57], indicating the increasing incompleteness of T-cells differentiation in parallel with a declining lymphocytes' number by age.

The differentiation of CD34 HSC migrated in the thymus from BM does not aim to produce only matured T-lymphocytes, but a continuum of stem-progenitor cells at different stages of aging, myeloid cells, young NK cells (+CD2 low, -CD3,

-CD5, -CD7), alike it is going in a BM [58]. The number of young CD90 and CD4 CD25 cells in the gland decreases by age 5.7-fold and 2.9-fold [59]. Besides this, up to 12% of immature cells are registered in the peripheral blood of healthy adults [60]. Most of post-thymic immature cells in the blood are cortisone sensitive and tend to apoptotic decay, being CD25-positive, *i.e.*- regulatory cells T reg [61]. The enigmatic stem CD34+TdT+ and CD34+CD4+ $\gamma\delta$TCR naive progenitors of T cells constituted a minor population in the peripheral blood, but their major subset is among tissue-residing and intraepithelial lymphocytes [62], which play versatile roles in tissue regeneration, inflammation, and autoimmune diseases, as assumed in [63]. However, the number of these cells is not enough for evaluation of the amount of their functional resource.

3.2. Telomeres

Circulating normal white blood cells have a minimal percentage of hematopoietic stem cells or multipotent progenitors (HSC-MPPs). Though they are found in many tissues as a main source of morphogenic activity across a life span, their telomeres' length (TL) are shortest compared with other tissues of the human body [64] [65]. Besides this, the rate of a loss of telomere length (TL) by age in lymphoid lineage (LL) two times (0 - 18 years age) and 1.5 times (19 - 100 years age) faster than in a myeloid lineage (ML) [66]. At the age 75 years old, the LL and ML lose 6 and 4 kbp (kilo base pair) telomere length, with exponential rates −0.03 and −0.022 per year, reducing the length of telomeres to 0.60 and 0.85 kbp. In the advanced part of life 75+ these telomeres reducing goes with more increased exponential rate −0.139 and −0.063 per year, correspondingly to [37]. Faster loss of reproduction capacity of LL vs ML confirms the fact, that lymphopoiesis is a most injurable lineage of hematopoietic system, stem cells of which are involved in the physiological or pathologic repair of the epithelial-endothelial spheres, circulating with blood into tissues [23] [24] [26] [37] [67] [68] [69] [70].

The strong loss of TL is very typical for advanced age of the healthy human as well, as for accelerated aging of the hosts with malignancy. The TL decay leads to either transient lymphopenia, or direct irreversible exhaustion of lymphopoiesis, followed by a temporal or insufficient forcing of proliferative processes in tissues, depending on the original level of a cell number in circulation [71] [72].

Thus, the viability of human is provided presumably by current proliferative resource (potency) of BM (CPR) described as a product of current HSC number and current capacity of cells to multiply, *i.e.* the length of their telomeres [48] [73]. The term a current proliferative resource of hematopoietic system (CPR) will be used further in the text.

3.3. Conclusion

This brief description of natural rules in hematopoiesis shows a permanent post-pubertal involution of both BM and gland by age. But the physiology of the thymus is not self-sufficient, it is submitted to the maternal bone marrow BM

activity at large. The aim of thymus is the provision of forced morphogenesis during the relatively short period of puberty age, than the production of the majority of old (matured) T lymphocytes as a basic pool of T-cells immunity.

The second substantial conclusion is that the peripheral blood contains a continuum of T-cells with transitional stages of their differentiation, *i.e.* levels of cells' aging. The composition of this continuum changes regularly along with the aging of the host. These unstable, natural cytological conditions, are quite provocative for alternative descriptions of the relation between lymphopoiesis and a bright range of pathologies, including cancer.

Nevertheless, irreversible and deadly loss of colony-forming HSC during whole body irradiation (WBI) < 1000 Gy provokes first the "hematopoietic" form of death in acute radiation syndrome (ARS), which lasts 1 - 1.5 months. Gastrointestinal and neurovascular forms of death appear after complete inactivation of the lymphopoietic system by doses > 1000 - 1200 Gy and last from tree days to several hours [74]. The strongly delayed period of the death during "hematopoietic" subsyndrome vs. two other ones is due to the mechanism of extra-support of an own somatic cell viability by morphogenic cells -migrants from BM and thymus.

The ARS, being a highly professional term at the beginning of radiobiology, was updated later in relation to the late effects of ARS as a multi-organ failure-dysfunction (MOF) [17] [75], which resulted from a late deficit of HSC in survivors. The term MOF after irradiation as well, after uptake of a chemical radiomimetics, as well as after the impact of anticancer compounds [76], had expanded later on entire pathology as multi-organ dysfunction syndrome (MODS) [77]. The essence of MODS is lymphopenia, nausea, dehydration, skin problems, alopecia, infertility, cardiomyopathy, bleeding, peripheral neuropathies, memory loss, osteoporosis and other symptoms of premature aging via loss of HSC, which are similar to mielosuppression induced by irradiation [78]. The same problems of an HSC' loss occur at many different diseases, including non-treated cancer, and senility (infirmity), after cancer radio-or chemotherapy. All these symptoms are similar and known as a "side effects, complications".

Thus, the facts show absurdity to percept the T-linage of lymphopoietic system as a defensive one only. Neglecting processes of cells' differentiation, *i.e.* the functional specificity of immature lymphocytes in stem and progenitor stages, the immunooncology took itself out of the general conception of lymphopoiesis, though it has to be only part of this system.

4. About Experiments

4.1. One-Sided Interpretation of Results

All models in experimental oncology have disproportionately high ratio of a mass of grafted malignancy toward mass of a host animal in comparison with a human. This specificity accentuates a successful competition of tumors with normal tissues for growth and energy resources of the host. The base metabolism closely relates to the body mass renewing, including the normal and pathological

types of reparation-regeneration, and general viability, *i.e.* life span [79]. Earlier we demonstrated a 5-times inhibition of the yields of radiogenic lymphomas in thymus of (C57Bl × CBA) F1 mice after the artificial decline of their metabolic activity by temporary substitution of intracellular water H_2O onto 30% D_2O, that leads to the more, than 6-times suppression of synthesis DNA in tissues before irradiation [80]. As a hydrogen bonds formed by deuterium are stronger than those formed by protium in total organism, this kind of metabolisms inhibition has not a chemical, but pure physical nature. Regardless decreases mitotic activity of immune cells too, the mass of grafted lung tumor RL67 in (C57Bl × CBA) F1 mice with substituted body water on 20%, 30% and 40% of D_2O decreases 4-fold, 8-fold and 11-fold in the two weeks. Then, why this result is quite opposite to expected prosperity of malignant developing due to inhibition of immunity? May a key metabolic factor of the mice influence of the growth of malignant allograft independently on immunity?

The widely used in immunooncology experimental models of athymic (nude) mice have strongly reduced number of matured lymphocytes, a reduced growth, general body weakness, and limited life span [81]. But the incidence and type of spontaneous tumors in them were comparable to those observed in phenotypically normal nu/+ and +/+ controls. This argues against the thymus dependence of the putative immunological surveillance mechanisms [82] [83] [84]. However, it is strongly ignored in experimental immunooncology. Other examples of influence of original status of the host viability on experimental malignant growth are given below.

Viability of a native host athymic nude mice (NM) is 2.2-fold lower (6 - 12 months), than that one of immunodeficient mutants (knockout) mice NSG (18 - 21 months). At 60th day after transplantation of human breast cancer cells, athymic nude mice NM show lower volume level of tumor growth engraftment (2.3-fold,) and number of metastases per mice (8.6-fold) vs. NSG mice [85]. Thus, a rate of malignant growth corresponds to general viability of the host organism, even though NM had more of WBC (2.6×10^9 vs 1.4×10^9 per l), lymphocytes (1.4×10^9 vs. 0.3×10^9 per l), and monocytes (4.5×10^7 vs 2×10^7 per l). This alogism (the more immune cells, the less viability, and vice versa) might be resolved, if the factor, which is responsible for the viability of the host, would be responsible for malignant growth as well.

The enhanced original viability of immunodeficient mutants (knockout) mice R2G2 (natural life span 2.5 - 3 years) vs. mice NSG (1 - 1.7 years) are proved by slower body weight loss (10% vs 25% per week), and better survival (median 14 vs 4 days) after 6 Gy whole body irradiation (WBI) [86]. Correspondingly, rate of growth of malignant xenograft (PNX0255) in R2G2 mice was faster (0.54 cm^3 per week) [86], than in NSG mice (0.24 ± 0.13 cm^3 per week) [87]. As both original strains have a similar rest of lymphocytes (mean 0.24×10^9 per l vs 0.3×10^9 per l), very low total fraction of T and B cells (3.3% vs 6.4% of WBC), and equal NK cells (0.3% vs. 0.3% of WBC), the tumor growth had depended on viability of a host.

Higher radio-resistance of R2G2 mice vs. NSG mice and illusive radio-resistance of cancer grafted to them, means that both normal and malignant tissues of mice had provided by one resource of hematopoietic stem cells (HSC), which are the main target for radiation. In fact, immunodeficient R2G2 mice had highly prominent extramedullary hematopoiesis in the spleen with an abundant number of large cells (11.28 ± 3.87 vs. 1.42 ± 0.13 per × 20 field; $p < 0.001$), which had had common markers for HSC and endothelial cells (CD31, CD34, CD41, CD105) [88] [89]. The quantity of these cells with a vasculogenic progenitor phenotype is the reason for the R2G2 mice's radio-resistance, and is responsible for the faster rate of malignant xenograft growth, slower body weight loss, and better survival after 6 Gy WBI.

Thus, the hematopoietic progenitors committed to an angio-vasculogenesis presumed to be a booster as a somatic growth, so too growth of a tumor, at the conditions of ultra-immunodeficiency. The difference is not explainable by any T-reg influences, since a knockout of IL-2 receptors has a place in both strains R2G2 and NSG.

Remarkably, the different number of CD34+, CD31+ markers for endothelial colony-forming cells (ECFCs) in natural human tissues is different [90]. The effectiveness of conventional myeloablative therapy of the cancers in corresponding organs is as effective, as the preexisting level of these markers in them (see below 5.3. CD34 cells in tissues and death rate). The lower viability of original NSG strain in comparing with R2 G2 ones can be due to lack of lymphoid stem cells enzymes, which resolve DNA strand breaks, particularly, terminal deoxynucleotidyl transferase (TdT) [53]. It may boost reparation-regeneration of sub-lethally injured cells after deliver enzymes into extracellular media from apoptotic immature lymphocytes, migrated in different organs. In 2022, a TdT was also detected in previously unappreciated lymphoid-primed myeloid progenitors, redefining the lympho-myeloid axis in human hematopoiesis [91]. Finally, progressive growth of the human tumor transplant occurred significantly less often in the mice that eventually developed spontaneous tumors than in the mice that showed no spontaneous tumor development [82]. This fact points to competition for host growth' resource, rather than presence of any antitumor activity. Thus, the matured T cells, being the opposite of quantity of the stem cells, can only imitate the own involvement in the control of tumor growth.

4.2. Conclusion

All considerations given above do not prove the mainstream in immune oncology. Though the bone marrow (BM) is the only primary source of lymphocytes in nude mice, they possess prothymocytes, and 3% - 6% of splenocytes are Thy-1-positive, [92]. The viability of both normal and malignant tissues in immunodeficient mice depends rather on the number of HSC and immature descendants of the lymphoid-myeloid axis, like CD 133, CD34 CD31, CD90, Thy-1, and TdT-positive cells. Stem cells are the main source, which provides cells of

the other histotypes to repair and regenerate damaged tissues and organs. They play essential roles in the pathophysiology of viability, aging, and various diseases, including malignancy [26] [93] [94] [95].

5. Cancer and Normal Tissues

5.1. A Growing Tumor and Fetus

The striking similarity between tumor growth and embryonic development is an appropriate model for identification of the cells, which promote an increasing biomass [19] [96]. The limitation of proliferative capacity CPR in humans shows the maternal mortality rate, which is 5-fold higher at the age of 40 years compared with 25 years old. Prenatal and postnatal periods may elucidate the nature of cells involved in normal and tumor morphogenesis.

The bigger volume of umbilical cord blood correlates with total count of CD34 hematopoietic stem cells ($p < 0.0001$), nucleated (young) red blood cells ($p < 0.0001$), larger placenta ($p = 0.001$), larger birth weight of the baby ($p < 0.0001$), and his viability ($p = 0.002$) [97]. Thus, the embryonic-like growth of the tumor's biomass imposes on the body a deadly competition for the natural morphogenic potency CPR of BM. An abnormal and irreversible loss of reproductive activity of the stem cell pool during cancer growth reduces the life span of the tumor's host, like the pregnant womanfolk, which breaks the harmful competition in time by a natural mechanism.

The biological role of young lymphocytes in somatic growth-morphogenesis illustrates a correlation between the dynamic of the fetus' weight and the weight of its thymus [98] as well as the increasing of the thymus mass (2.5-fold), body mass (2.7-fold), and total blood lymphocytes (2,2-fold) of newborn babies during the first postnatal year, as it follows from [31] [33] [99] [100] [101] [102] [103]. Conversely, lymphocyte number decreases to the normal level of adults at 18 and continues to drop up to death, along with the slow involution of a fat-free mass of the body [33] [99].

5.2. Angiogenesis

The CD34 and CD133 HSC-markers are involved in normal morphogenesis, being presented on mesenchymal cells, muscle satellite cells, corneal keratocytes, interstitial cells, epithelial progenitors, vascular endothelial progenitors, and activated endothelial cells. They present in different tumors, as well [104]. The stem cells CD133 and CD34 exist in adult hearts, decreasing their prevalence during aging [105] [106]. The endothelial progenitor cells, *i.e.* an angioblast sells with hematopoietic stem cells marker CD133, CD34, and VEGFR 2 in blood, loss of CD133 during partial differentiation, and gain the expression of CD31 angiogenic-endothelial marker, remaining the immature CD34+ stem vasculogenic progenitors [39] [107] [108] [109] [110]. Can't these properties be a focus of attention instead saga about killers and numerous cells that interfere with killers [111]? Cancer hypoxia weakens the homing of tumor cells and triggers their

escape from the hostile environment into circulation in search of more oxygenated nourished tissues. This process associates with more aggressive tumor phenotype.

Essentially, the non-specific general hematodepression is the main sign in non-treated patients with advanced cancer. Chronic inflammation symptoms (CIS) are a universal, multi-original sign of an exhausting of proliferation in bone marrow after its inevitable overloading. The chain of general symptoms: myelosuppression, abnormal metabolic base rate (MBR), lymphopenia, body weight loss (BWL), frailty, and death, are common for natural aging or radiation aging [78] [112] as well, as for advanced cancer as such [113], for cancer cytotoxic therapy [114] [115] [116], and even for eclampsia of third trimester of pregnancy [117] [118] [119].

5.3. Deadly Competition

The higher the number of tumor-infiltrating lymphocytes, which are inseparable from HSC [120], the longer recurrence-free survival (RFS) and less the metastases in terms of N0/N1-2 [121]. The higher the level of the vasculogenic marker CD31, the earlier the tumor is found in terms of TNM [122]. Thus, the lower the number of lymphocytes infiltrating tumors that exist, the greater the degree of hypoxia, the weaker the homing of tumor cells, and the greater the probability of their migration to more vascularized regions are. The migrating HSC and progenitor cells are real sponsors of cancer, and a prevention of collaboration between them is rather a more reliable approach, than a killing of malignant cells in situ. Even 27% of excess death from secondary malignancies and 14% of a recurrence after HSC' transplantation point on morphogenic influence of circulating cells of bone marrow origin, especially vs. only 11% of excess death for a chronic graft-versus-host disease [123]. Importantly, the non-treated cancers are followed by lymphopenia [1] [124] and by paraneoplastic inflammatory syndromes (PIS), which is a sign of either an undiagnosed malignancy or a cancer recurrence. A PIS, in turn, are associated with myelodysplastic syndrome (MDS) [125]. The essence of PIS, MDS, as well, as ARS, MOF and MODS are the varying results of hematopoietic exhaustion, which is harmful for normal tissues. It arises after preliminary phase of CD34 + HSC' excessive mobilization during abnormal tissues growth, reparation-regeneration, and healing the wounds, and manifests itself by lymphopenia. Actually, the side effects or complications are the result of the cancer wins in competition with normal tissues for morphogenic resource of HSC.

Alas, a dominant convenient misconception continues to dictate that cancer can be nothing but an enemy, so the enemy is the target of immunity. In reality, most of the mechanisms of cells immunity in oncology reflect the activity of the main mechanism, which is morphogenesis with CD34, CD133 stem cells and their diverse descendants-progenitors of lymphoid lineage [126] [127]. They are the main targets today for the toxic therapy, which are based on indirect weakening of morphogenic support of a tumor.

5.4. CD34 Cells in Tissues and Death Rate

The universal trophic, morphogenic influence of young mononuclear cells on malignant growth noted by individual scientists in a long history of oncology [128]. Universal morphogenic properties of stem and progenitor cells from bone marrow (BM) and umbilical cord have proved by recent clinical transplantation of these cells for the treatment of human diseases, including neurological disorders, pulmonary dysfunctions, metabolic-related diseases, reproductive disorders, skin burns, cardiovascular and another organ's dysfunction [129]. The HSC utilization, being universal in terms of consequences, is different in origin. Apart from direct killing of CD34 cells, they can be either extensively mobilized from BM into normal tissue for a renewal, or in a growing tumor' tissue [130], or extensively transform into of next immature descendant, for example, Treg.

Light hypocellular bone marrow status, accompanied by MDS, can be relieved partially by the precourses of DNA. Subsequent improvement of the patient's general conditions and drastically increasing the frequency of Treg cells in PB [125] compromise completely a generally accepted immunosuppressive function of these immature cells, but prove their morphogenic/trophic properties in relation to the normal tissues of the body.

The number of CD34 markers of HSC dominate in normal tissues (5 - 30 fold) over CD2 marker of T-cells, oppositely to their distribution in peripheral blood. The normal tissues with relatively higher markers ratio (CD34, CD31): CD2 ≈ 34, accompanied by better survival of a host in the case of their malignization in the future. And vice versa, a worse survival will happen in cancer patients if potential targets for próximo malignization have been normal tissues with a lower ratio (CD34, CD31): CD2 ≈ 5.4 in them. Markers of HSC CD34 with CD31 is typical for angio-vasculogenic progenitors [127]. They provide a favorite condition for prolongation of local tumor growth, without a distant spreading (M0 in terms of TNM classification), and thereby contribute to enhance of probability for registration of earlier stage at diagnosis. In case of malignization, the tissues with the highest natural CD34: CD25 Treg ratio followed with high survival (90% - 50% during the age 25 - 90 years). A malignization of normal tissue with lowest CD34: CD25 Treg ratio followed lower general survival (35% - 4% during the age 25 - 90 years) [131]. Thus, it seems that the presence of CD34 and CD31 stem cells in tissues can promote malignant growth, though CD2, CD25 Treg cells also manifest this [131] [132].

Depending on the current level of myelosuppression, and independently on its origin, the ratio CD34 to the descendants of T-lineage either can be kept relatively stable, with the physiological (asymmetric) type of cells division, or the turbulent, insufficient, symmetric one (**Figure 4**, for instance) [48] [49].

In the first type, one of two stem cells, produced simultaneously, is differentiating. In the second type, the replenishment of stem cells pool, or differentiating pool cell goes consecutively, dominating by turns [133].

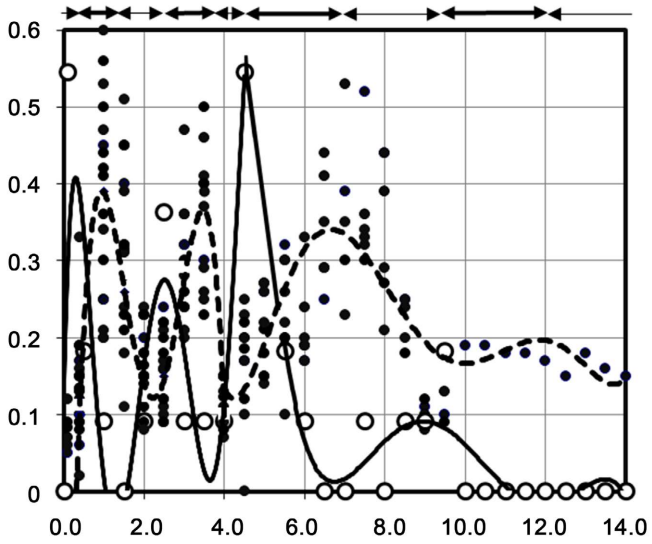

Figure 4. The periodic changes of CD34 stem cells number in blood of cancer patients and their rate of death along with a reduction of average life span [46] [134]. Abscissa: average life span, months. Ordinate: black points: number of circulating CD34 stem cells (% of mononuclear cells); white points- part of death during each half month (relative units × 3). Dotted line-average value of CD34 is approximated by 6-degree polynomic ($p < 0.001$); Solid line-part of death is approximated by 6-degree polynomic ($p = 0.002$). Double-arrows show the lag time elapsed between pike of HSC and the delayed pike of death' rate.

The result of imbalanced (symmetric) hematopoiesis is prognostically poor, and leads to an increase of neutrophil to lymphocyte ratio (NLR) in blood. NLR, which is above the physiological level, has been accepted as a universal measure of harm to the health of the entire pathology [135]. During one month of conventional treatment of patients with oropharyngeal cancer, the ratio of the values of myeloid CD34 cells to lymphoid CD34 cells increases 2-time ($p = 0.04$), proving the responsibility of stem cells for values of NLR in blood, and their high susceptibility to the damages. [46] [134] [135].

There is no doubt, that fluctuations in stem cell numbers are a sign of accelerated exhaustion of proliferating resource of BM. The peaks of a number of CD34 cells outstrip the peaks of death rate on **Figure 4**. If we consider the lags between the nearest maximums-minimums of both parameters, the direct dependence of the rate of death (y) for CD34 level in the blood (x) becomes obvious: $y = 0.5425x - 0.0669$; $R^2 = 0.7832$ $p = 0.0045$.

Each preceding relapse-free period, during which the stem cells are outside a tumor, is favorable for the imitation of an optimistic prognosis. [136]. However, a lag time between pics of both parameters (horizontal arrows in **Figure 4**) are reducing along with shortening life span. Dispersion of mean CD34 values in terms of standard deviation (SD) enhances exponentially from 17 to 0.4 months of life span ($SD = 0.09e^{0.113t}$; $R^2 = 0.5$; $p = 0.001$), reflecting a 6-fold progressive increase of turbulence, *i.e.* an enhancing the symmetric component in system of HSC reproduction [46] [48]. The shortening of lag values is a true measure of

treatment's harm for the host also. The pathophysiological fluctuation of tumor volume can be wrongly interpreted as a complete remission (CR) or progression of disease (PD) and could easily provoke imaginations about specific, "help - suppress" type of immune activity [48] [137] [138]. In reality, what does kill the patient is not the primary tumor, but the metastasis. Their probability enhances in cases of recurrent growth of a primary tumor.

6. Therapy

6.1. What Is the Matter of Cancer Death

An overestimation of the commitment of the T lineage of lymphopoiesis to fight guides the followers to neglect of functional hierarchy of cells with different maturity, *i.e.* aging. The stumbling block of immune-oncology lies in ignoring the variety-diversity of numbers of immature cells involved in well-studied negative reactions of BM. All of these reactions predestine in many cancer patients initially, and are just getting worse during a treatment.

Why the benefit of cancer treatment could not be a result of simple ceased trophic-morphogenic connectivity between lymphopoiesis and growing tumor itsel? In fact, it is going with normal tissues at the state of "complications", with some pregnant women, which have exhausted hematopoiesis during third trimester, or with the whole tissues of a body during chronic exhaustion of lymphopoiesis by whole life irradiation with low dose rate [14] [119] [139] [140] [141].

Figure 5 shows, that the rate of death in terminal part of natural life is −0.33 per year, being much faster than in previous period between 40 - 80 years age (−0.01 per year; $y = 1e^{-0.01x}$, $R^2 = 0.8$ p = 0.001).

The "radiation aging" because of whole life irradiation with daily dose rate 0.003, 0.008 0.018, 0.038, 0.075, 0.128, and 0.263 Gy for total body have the same average terminal rate of death, independently of dose rate (−0.31 ± 0.116 ± 0.052 per year, n = 6). A similarity means, that exhaustion of the most damaged system lymphopoiesis is a common, universal reason for loss of the life span (**Figure 5**). High (terminal) rate of natural death lasts around 15 years in humans, that is comparable with best, but rare results of the therapy of an advanced cancer.

Results of conventional therapy in terms of 5- and 10-year survival for population US according to SEER statistics [142] [143] leads to conclusion that treated patients are dying according to universal mechanism of terminal aging, independently of age at diagnosis (**Figure 6**).

Accordingly, the conventional therapy as such is unable to overcome this essence of a cancer and is capable only of its modest modification. The averaged for five ages, rate of death of patients with lung and colon cancers are faster (−0.34 ± 0.13), or the same (−0.22 ± 0.07) vs. natural one for terminal part of life (−0.23 per year). The average rates of death for melanoma, a breast, and a prostate cancer (−0.17 ± 0.05, −0.15 ± 0.04, and −0.13 ± 0.05) are a little bit slower

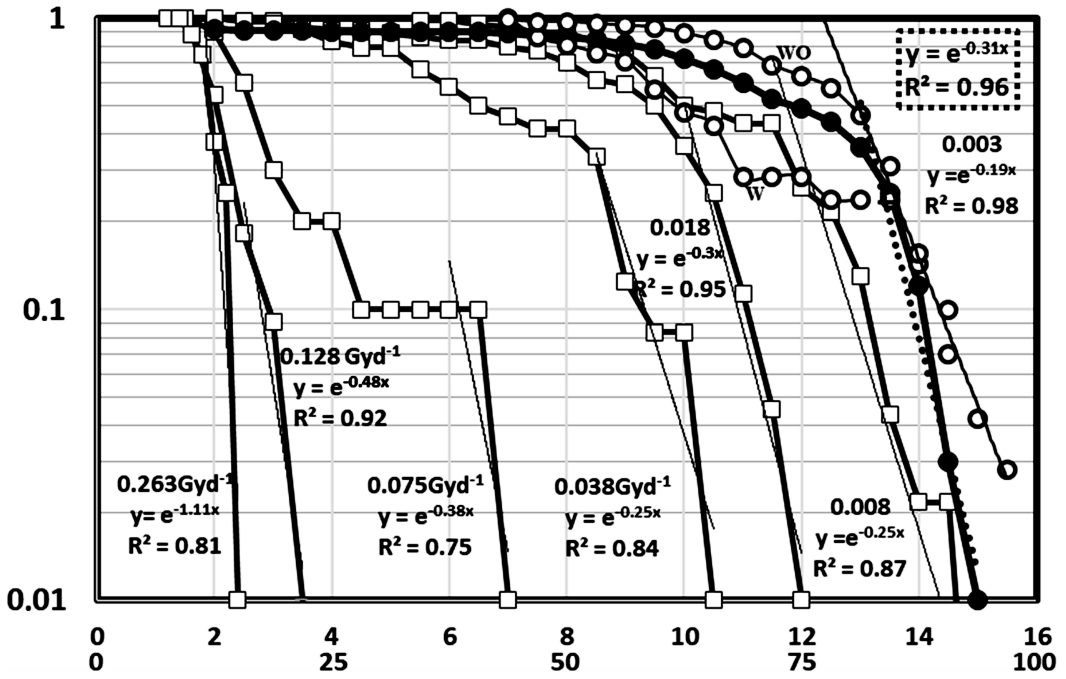

Figure 5. Radiation aging in comparison with natural aging in the Beagle dogs. Abscissa: Age, years (lower scales is for humans). Ordinate: Survival, relative units. Black symbols are for curve of natural aging (thick solid line); White symbols are for curves of radiation aging under chronic (during a life) exposure (thin solid lines), with a daily dose rate: 0.003 Gy (circles; two subgroups of these dogs, WO and W, are shown separately, according to the **Table 1**), 0.008, 0.018, 0.038, 0.075, 0.128, 0.263 Gy (squares), and $\leq 1 \times 10^{-5}$ Gy daily (control). The average terminal exponential rate of death(M) of all subjects exposed at the dose rates −0.003 - 0.128 Gy daily is M= −0.308 ± 0.105 (for humans), *i.e.* it is comparable to the natural death rate for population: −0.31 year^{-1} [141].

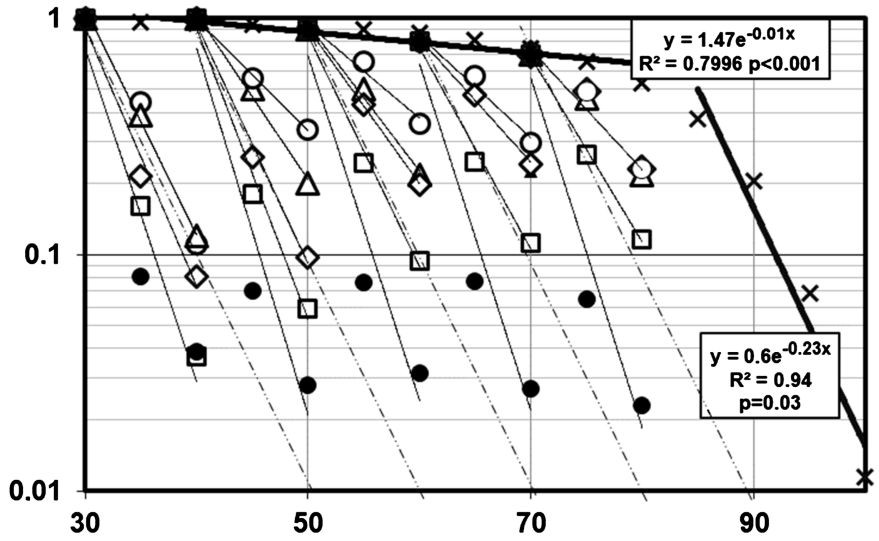

Figure 6. The 5- and 10-year survival of US patients with cancer diagnosed at 30 - 70 age and conventionally treated, in comparing with natural survival of whole US population. Abscissa: age, years. Ordinate: survival, relative units. X-symbols-control population. Cancers: lung (dark circles), colon (square), melanoma (rhombuses), breast (triangle), and prostate (white circles). Dotted line-replica of terminal period of natural (control) survival with exponential rate of death −0.23 per year [142] [143].

(less, than 2 times) to the terminal natural rate −0.23 per year, reflecting the modest positive contribution of conventional treatment. However, all the rates of cancers death, between 40 - 80 years age are too much faster (17 - 13 times), than the rate of natural death, which is −0.01 per year ($y = 1e^{-0.01x}$, $R^2 = 0.8$, $p = 0.001$). Thus, the cancer, as such, predetermines deadly exhaustion of lymphopoiesis before diagnosis and treatment, as a long-term irradiation did (**Figure 5**).

The lowest dose rate 0.003 Gy per day (**Figure 5**) provides the average whole-life total dose of dogs around 10 Gy, which are of 20 - 30 times more, than average permitted (background) dose for the humans. Nevertheless, this experimental condition is relatively mild, and could be classified as that, which provides hormesis phenomenon, for part of the weakest animals (WO) at list [144]. It is approximate to the mode of therapy titled "metronomic" [145] [146]. They are resonating also with competition between growing tumors and healing wound [146].

Along with inevitable lymphopenia induced by cancer and by all kinds of conventional "therapy" [147], from 50% to 90% of patients' loss of body weight in response to treatment with concomitant cachexia, gastrointestinal, cardiovascular, respiratory, infectious, renal complications, reduction quality of life and even survival [1] [4] [147] [148] [149]. Moreover, the therapy contributes to the emergence of new malignant tumors, [3] [14] [150] [151].

Lymphopenia serves as a rough prognostic biodosimeter for death after irradiation. The reason for that is the supersensitivity of lymphopoietic lineage of hematopoiesis (CD34, TdT) toward any damaging factors, and thus, it is responsible for the health of a whole body, independently an origin of the cause [152] [153]. More precisely, lymphopenia reflects roughly the level of exhaustion of a lymphopoietic (proliferative) resource CPR, which can be the current product of an average lymphoid stem cell number by their average telomeres' length, or by average mitotic activity [48].

Thus, the host organism supports selectively the tumor growth, alike a fetus in pregnancy, by circulating morphogenic cells. An exhausting of their resource limited naturally by an abnormally long extra-renewal of malignant tissue, is incompatible with normal tissues' viability and normal life span at large. At the same time the violent cytotoxic therapy makes only temporal illusion of a complete or partial remission (CR, PR), lowering current proliferative resource CPR of HSC.

6.2. Limitation of Cancer Treatment

The conclusion given above solved the challenge, situated in immune oncology till now, namely that a treatment's benefit is accompanied by additional lymphopenia. Since the therapeutic application of nitrogen mustard in 1949, described by S. Hazel in 2014, conventional treatment of cancer with cytotoxic agents (radiotherapy, chemotherapy, and targeting therapy) induces additional lymphopenia, as authorized by the NCI and WHO in the "adverse" phenomenon of the conventional management of solid tumors [16].

An abnormally high metabolic rate of cancer can provoke lymphopenia before treatment also, as it happens during abnormal or prolonged pregnancy. Around 20% - 70% of patients before treatment have $<1 \times 10^9$ cells per l already, manifesting a life-threatening [1].

According to the NCI WHO and Center for Disease Control and Prevention, oncology has a deal with moderate ($\geq 1 \times 10^9$ per l), severe (≤ 1 - 0.5×10^9 per l), very severe (≤ 0.5 - 0.1×10^9 per l) and lethal ($<0.1 \times 10^9$ per l) lymphopenia [16]. These levels correspond to acute radiation injury at the WBI with doses < 1 - 2 Gy (moderate, death may occur 0% - 5%), ≥2 - 4 Gy (severe, 5% - 50% of death), ≥4 - 8 Gy (very severe, 50% - 100% of death), ≥8 Gy (100% deadly ones) [74]. Only limited injury of lymphopoiesis $\geq 1 \times 10^9$ per l, being registered either prior, or during treatment, coexists with the benefit of tumor's control for each tumor type, whereas the level $< 1 \times 10^9$ per l compromises the benefit's outcome [147] [149] [154] [155] [156] [157] [158].

6.3. Why Only Mild Lymphopenia?

A benefit of tumor' control in terms of lethality is possible along with moderate absolute lymphopenia only, nausea (5% - 50%), headache, fatigue, weakness, which is equivalent to whole body irradiation at dose not more, than 2 Gy for healthy person [159] [160]. A moderate lymphopenia $\geq 1 \times 10^9$ per l, provoked by cytotoxic treatment first, persists only temporary, letting the tumor get worse until the lymphopoiesis restores itself, and a doctor can repeat the cytotoxic impact. However, the lymphopoiesis is not a perpetual engine, and each next injury leads to exhaustion of the current proliferative resource (CPR) of the system limited individually by born [48].

Complete remission as "no evidence of disease (NED)" doesn't mean a healing, because NED becomes legitimate already if it lasts only 1 month. This short lag time is officially used for the evaluation of results of treatment in terms CR, PR, SD, and PD, and coincides with an average duration of cycle "injury-partial recovery" in BM stem cells [137]. The terms "benefit" or "response" are nothing more than a formality, because the lifespan after several courses of therapy becomes much shorter than their natural limit by age (**Figure 5** and **Figure 6**). It explains, why the criterion "survival" universally accepted in oncology is so modest: 1 - 5 years [48]. The number of those, who survive 25 - 30 years, are less than 7-times [161]. The comparison of equivalents between "lymphopenia, radiation dose, viability" suggests that the benefit of a treatment stems from the inhibition of normal lymphopoiesis. In fact, lymphoid tissues are more sensitive than tissues of other histotypes [152] [153]. The optimal dose-equivalent of one treatment' cycle 1 - 2 Gy is more harmful for lymphopoiesis than for any solid tissues in terms of their repopulation, including non-system, solid tumors. At local therapy, a minimal cycle-equivalent dose > 20 - 30 Gy needs to get an "answer" of a solid tumor volume [162]. This local dose is quite harmful for hematopoietic mononuclear cells, which participate in the tumor progression by fostering angiogenesis at list, as it shown by [163] [164]. Hence, the wellbeing of the

BM reproductive system and thymus directly determines the reproductive activity in tumors initially and only later in normal tissues, according to the residual principle. A longer lymphocytes' telomeres associate with more risk of cancer development overall (breast, rectal, prostate, pancreatic cancer and lung adenocarcinoma), but with a less risk of non-cancer related death resulted from slight reduced metabolic activity [165] [166].

Deep lymphopenia in general pathology is harmful for viability of the host and his tissues. People diagnosed with cancer, lose weight because the process of cancer cells dividing uses up a lot of energy. Fat-free weight loss in %, occurring prior to the initiation of therapy is predictive for short median survival of cancer patients, independently of disease stage and patient performance status (months = $27e^{-0.104\%}$; p = 0.0025) [167]. Association between malnutrition - undernutrition and total lymphocytes count (TLC < 1.2×10^9 cell per l) accompanies by 2-fold decrease in plasma albumin content and somatic growths retardation [168] [169]. At mild lymphopenia ≥ 1×10^9 cell per l after total irradiation of the body of healthy persons, the probability of death is 0% - 5%, because of metabolic-threatening of the organs and tissues, including malignant ones. In terms of pathophysiology, the relative lymphopenia (≥1×10^9 per l ≤ 1.5×10^9 per l) and severe lymphopenia (≤1×10^9 per l) among the 31,178 participants from US with median age were associated with the corresponding risks of mortality 1.3 and 1.8, including cardiovascular disease > 34%, angina > 8%, chronic bronchitis > 8%, arthritis > 8%, emphysema > 8%, liver disease > 8%, thyroid condition > 8%, and cancer > 8%. Lymphopenia was also associated with worse survival in multivariable models, including traditional clinical risk factors. Herewith, ten-year mortality ranged from 3.8% to 62.1%, depending on the current status of lymphopenia [170].

Thus, it is quite reasonable to associate non-lethal lymphocytopenia > 1×10^9 cells per l with the deterioration of the renewal not only of normal tissue (side effects), but tumor tissues also. The cytotoxic therapy at lymphocytopenia < 1×10^9 cells per l is useless for the control of tumor progression and dangerous for viability of normal tissues and a host at large. However, any changes of circulating lymphocytes parameters as well as all syndromes ARS, MOF, and MODS just reflect the main pathognomonic changes of the current proliferative resource CPR of the hematopoietic stem cells pools (CD133, CD34, TdT, HSC) [93] [95] [171]-[176].

6.4. What Is "Stimulation of Anti-Cancer Immunity"

The idea of a redistribution of circulating morphogenic cells from tumor for reparation of sublethal injuries in normal tissue we used for the interpretation of B. L. Cohen's shocking data (1997) about the decline of lung cancer incidence vs. enhance of mean radon level in US counties [80]. Later we analyzed two groups of Beagle dogs, with (W) clinically recorded benign tumors or tumors of unknown nature (palpable/visible), and group without these symptoms during 10 years of life (WO) [144]. The non-irradiated control W dogs lived longer than

control dogs WO (11.8 ± 0.34 vs 10.7 ± 0.43 years; p ≤ 0.05). The control W dogs have a lower exponential death' rate of -k, and bigger percentages of solid cancers, inflammation, and atrophies by autopsy (**Table 1**).

The data pointed to the dependence of spontaneous malignization on the capac-ity of cells' renewal in normal organisms, which, in turn, depends on stem cells proliferative resource CPR, evaluated by us as a current product of stem cells number and their average doubling activity expressed as either Hyflick's limit, or DNA synthesis, or length of telomeres [48].

So, the wicker non-irradiated dogs WO with shorter stem cells' resource, in comparing with normal population W, live shorter and have the less number of benign and unknown tumors during ten years of life. Then, the artificial weakening of CPR, *i.e.* trophic connection between BM and tissues, looks like a kay point of a tumor growths control, especially in the weakened subjects.

Table 1. Control and low dose chronically irradiated dogs (0.003 Gy daily, during whole life) without palpable/visible tumors of unknown nature (WO), and with them (W), during first 10 years of life.

Dose	0 mGy·day^{-1}		3 mGy·day^{-1}		p
Subgroups of dogs*	WO_0	W_0	WO_3: WO_0	W_3: W_0	
Average life span, years	10.7	11.8	1.10	0.97	p ≤ 0.05
Body Weight loss, %	15	21	2.13	0.90	p ≤ 0.05
Cancer (autopsy), %	39.5	60**	1.14	0.97	
Hematoblastoses, %	9.4	6.8	0	1.0	p ≤ 0.05
Anemia, %	2.1	6.8	0	0	
Inflammation, %	57	75***	0.46	0.47	
Diarrhea, %	52	51	1.48	1.49	
Vomiting, %	50	41	1.88	2.27	
Metaplasia, %	1	0	19	>17	
Atrophy, %	9.3	19***	6.6	2.68	p ≤ 0.001
$-k_1$ year^{-1}	1.22	1.22	0.65	0.72	p ≤ 0.001
$-k_2$ year^{-1}	0.078	0.028***	0.33	0.45	p ≤ 0.001
Reduced appetite, %	19	23	1.21	1.83	p ≤ 0.001
Dogs, which are with (W) tumors benign or unknown nature (clinically), or without them (WO) during 10 years of life.	0	100***	0	100***	p ≤ 0.001

*Without or With - according to clinically recorded (palpable/visible)during first 10years of life the benign tumors or tumors of unknown nature, %;the-k_1 and -k_2 are exponential rates of death during initial (1) and final (2) parts of life[144]. Original Data acquired by the Argonne National Laboratory (Lemont, IL, USA) were extracted from the "γ-Beagle Dog Tissue Archive". We examined data stored as: "Life span: Whole Life Gamma Irradiation, External Co-60 gamma-ray exposure, continued until death on13-month-old dogs of both sexes" (http://janus.northwestern.edu/dog_tissues/introduction.php). **p ≤ 0.01; ***p ≤ 0.001.

Table 1 shows also, that irradiation during whole life (0.003 Gy daily) increases the percentage of those with body weight loss and with dystrophies among of WO dogs. Despite that, life span of irradiated WO dogs is extended (+10%), rather because of the elimination of late (after 10 years of life) hematoblastosess. However, the elongation of life span in irradiated WO dogs does not exceed the average normal level (11.8 ± 0.34), which is typical for control W-group. These data do not permit to consider the phenomenon as stimulation, especially since it appears inside a part WO of whole population only.

The state of frailty (weakness) presents among patients with advanced cancer. The deficit of HSC after cancer therapy is an obvious phenomenon. Sometimes it demands additional stem cells infusion for partial reconstruction of an injured hematopoiesis [177]. We interpret the elongation of life span in originally weaker irradiated animals WO (**Table 1**) as a switching of morphogenic cells of BM origin toward reparation-regeneration of a numerous non-lethal injures, induced by long term irradiation in the majority of normal cells of the whole body. Key point is that a nature of injures cannot be a lethal for cells at a very low dose rate (0.003 Gy per day), and all of them become a potential target for reparation, as it goes according to the rules of radiobiology. The redistribution of trophic cells from tumorigenesis to the reparation of injuries in normal tissue cells is more detectable at conditions of original shortage-slight deficit of trophic cells, *i.e.* deficiency of CPR, like in the dogs WO. Oppositely, at an original fullness of proliferative potency of the hosts, like it is in W' dogs, there are no needs for redistribution of CPR. On the other hand, at a dose rate of 0.008 Gy per day, we did not receive any signs of "stimulation" of the life span in both the irradiated WO and W groups. Their CPR both were reduced too much, since lifespan decreased by 8% equally compared to the corresponding control groups. [141] [144]. It means, that the optimal range of low-dose irradiation is narrow. Approximately, it has to correspond to the maximal number of sublethal injuries of cells and the minimal number of cell death in lymphoid lineage. It is very doubtful to expect more severe damage of any tissues, which are responsible for saving of a life, than natural lymphopoietic system [152] [153]. For instance, proliferative activity (Ki-67) in normal BM is higher (52.8% ± 9.2 SD) [178], than median one for breast cancer (22.3% - 30%) [179]. Therefore, the limitation of a dose, which is optimal for hormesis' phenomenon, relates mainly to morphogenic cells of lymphopoietic system, which redistribute competitively outward of a tumor toward normal tissues with reparable nonlethal injures in their numerous cells. The data in **Table 1** disprove the myth, that the "stimulation of immunity against cancer" is based of the hormesis phenomenon [180] [181]. "Hormesis" phenomenon has appeared selectively, in the wicked only, alike a slowing down of cancer death rate among the patients at advanced age +65 (**Figure 7**).

The acceleration of the exponential rate of death from non-malignant diseases, and competitive deceleration of the rate of death from cancer appears after the age of 60 - 65 in the entire populations, confirming a trophic deficiency, which is typical for advanced age. Thus, as a weakening of immunity in old population is

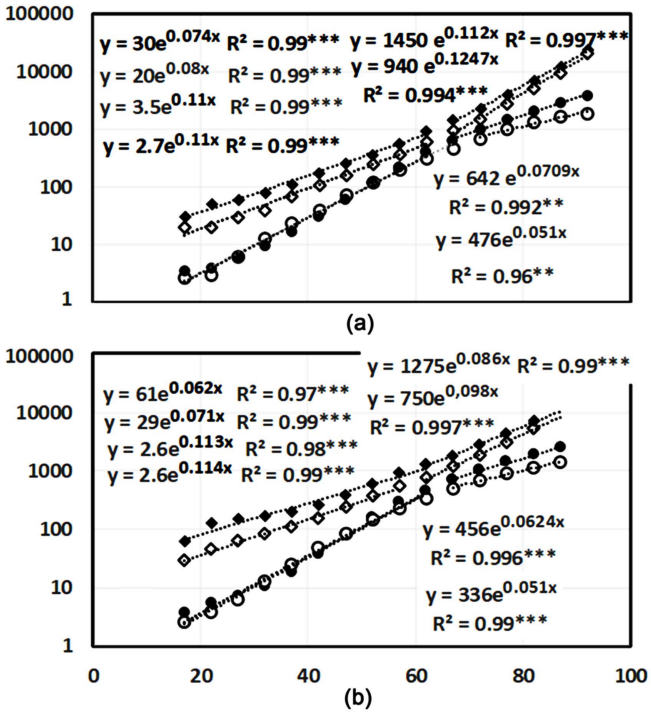

Figure 7. Death rates measured per 100,000 individuals for cancer and non-cancer diseases in the population of UK (a) and white population of US (b) by age and sex. Abscissa: age, year; Ordinate: rate of death per 10^5. Rhombuses- non-malignant diseases. Circles- cancer; Black symbols -male and white symbols- females. Dotted lines correspond to equations: $y = Ae^{\lambda x}$, where y is a rate of death per 10^5 persons, λ-exponential rate, per year; x-age, year; A-the value of y at the start of each of two age-periods: from 16 - 19 to 62 - 65 and from 65 to 80 - 85 years old. The equations for the 16 - 65 period are in the left vertical columns, and these for period 65+ are in the right vertical columns. The vertical range of equations corresponds to positions of the dotted line. The asterisks *** is $p \leq 0.001$ (from [182]).

a truism, the data in **Figure 7** disprove the idea of fighting with tumors [182]. The false phenomena of "stimulation" of anticancer immunity in +60 patients is result of natural destraction (pulling) of the scarce morphogenic cells from tumor and redirection them to reparation/regeneration of an escalating age-related problems in cells of normal tissues of the subjects with most exhausted morphogenic resource CPR only. The "stimulation of anti-cancer immunity" is the speculative term or code word, which do not describe a mechanism, but the result, *i.e.* is ad hoc.

7. Perspectives

All data considered above show, that tissues of any origin cannot proliferate without lymphocytes. The lymphopoiesis of the dogs and their radioresistance is lowest among mammals and similar with those in humans [183]. **Figure 8** confirms this truth by comparing the 52 populations of breed dogs with very different average body weight, life span, number of blood lymphocytes and rate of death from cancer.

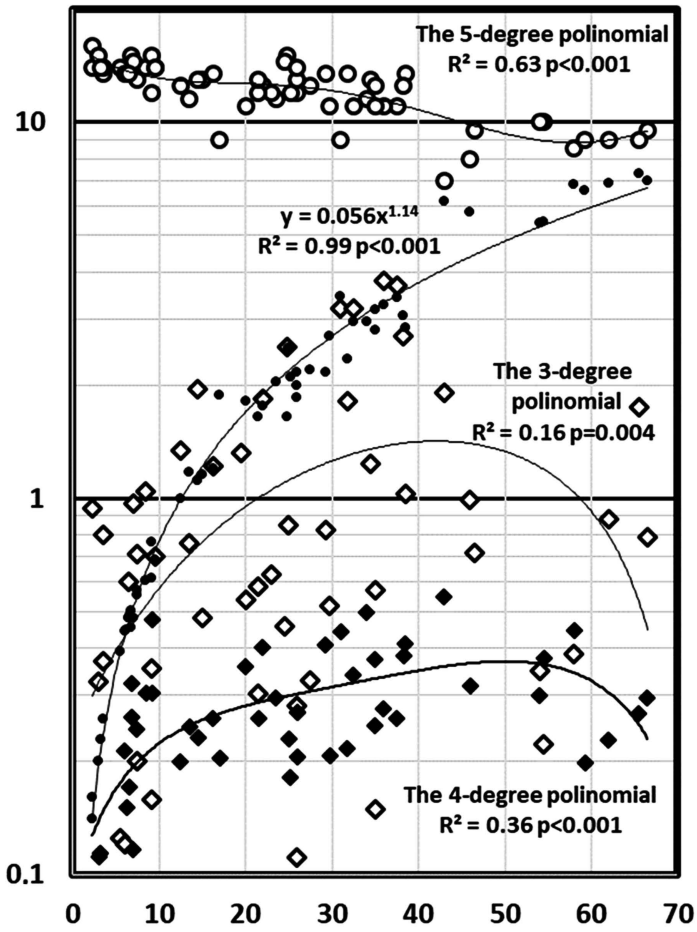

Figure 8. The interrelations between an average rate of body mass growth, a blood lymphocytes number, and cancer mortality' rate in the fifty-two populations of breed dogs, according data extracted from [184] [185] [186]. Abscissa: Average body weight (ABW) of breed dogs, kg. Ordinate: average life span (ALS, white circles), years; average rate of the body mass growth (black circles), as ABW: ALS, relative units; average lymphocytes' number in a blood (ALN, white rhombuses), $\times 10^9$ per l; rate of cancer death in the populations (CDR, black rhombuses), relative units.

The brief consequences of **Figure 8** are: 1) The well-known decrease in the LS of a big dogs in comparison with small ones associates with a high rate of body mass growth in them. 2) The high rate of body mass growth leads to accelerating exhaustion of lymphopoiesis. 3) The exhaustion of lymphopoiesis follows by a relative decline of a cancer death rate. 4) Average cancer death' rate (CDR) in the populations is proportional directly to average number of bloods lymphocytes ALN (CDR = 0.0242 ln × ALN + 0.285; $R^2 = 0.08$ p = 0.035).

True goal of therapy of advanced cancers is to save proliferative resource CPR of a host as equivalent of his viability, instead a destruction of HSC, aiming to get a short-term tumor response. Currently, there exists solely one method to accomplish this. It is protracted redirection of residual morphogenic hematopoietic stem cells and progenitor cells from the malignant tissue to repair sub-lethal damages in cells of normal tissues, created artificially.

Figure 9 shows the formal summary of the realistic nature of modern therapeutic phenomena based on partial inhibition of the current hematopoietic proliferative resource (CPR), *i.e.* reproductive activity of lymphopopoiesis. Its intensive declining during advanced phase of tumor developing and a cytotoxic therapy is designed on Figure 9 as the black areas "HR" symbolized a current sum (Σ) or integral of the product $\prod = HSC_i \times ND_i$, where "*i*" is a current number of HSC in each subject *i*, and HL is his current Hayflick limit. ND is a the number of stem cell divisions that each stem cell will do in the future (range from 60 - 40 times at the born to 1 - 0 at the cells death). The CPR is irreversibly decreasing, much slower with natural senescence in comparing with natural senescence complicated by malignancy.

Figure 9(a) reproduces the case, when after the previous course of the therapy the rest of hematopoietic resource CPR is as much, as it seems enough for repeated performance (black area CPR = 1.75 on Figure 9(a). Dotted lines are delayed survival as result of irreversible inhibition of part CPR, followed by timely inhibition of a tumor's morphogenesis, which is potentiating by circulating hematopoietic stem and progenitor cells.

Figure 9(b) reproduces the case of almost complete exhaustion of HSC-resource CPR after previous courses of cytotoxic treatment (black area CPR = 1.2). The both cases are concerned a direct inactivation of HSC, at a corresponding blood lymphocytes number $< 1 \times 10^9$, and $<<1 \times 10^9$ per l.

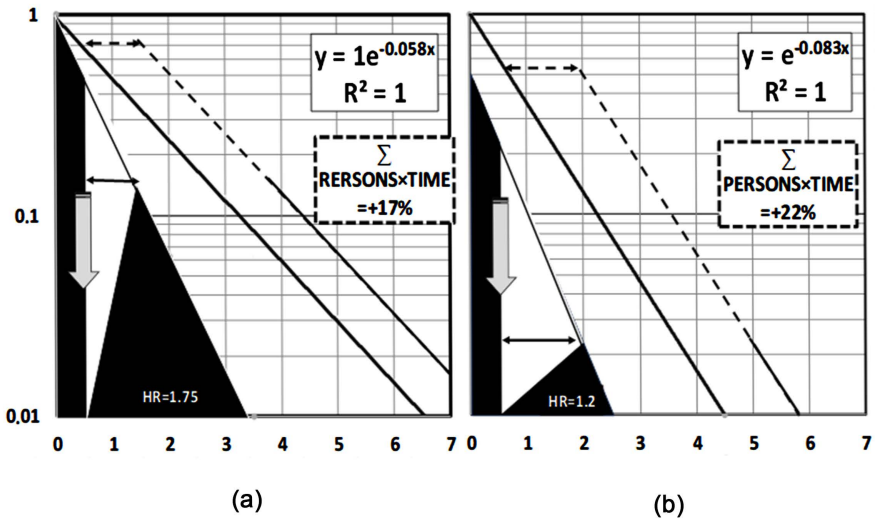

Figure 9. General schemes for effect of conventional treatment on hematopoiesis and survival of cancer patients, which are perspective for repeated course yet (a), and are not (b). Abscissa: time, years. Ordinate: survival, relative units. Black area HR: natural natural proliferative resource of hematopoietic system (CPR), as an integral of the number of active HSC by their Hayflick's limit in the patients, relative units. White areas show a consequence of conventional cytotoxic treatment, as a block and partial recovery of CPR. Gray arrows show the start of therapy, double-arrows show a time elapsed between start of treatment and incomplete recovery of the CPR. Thick solid lines present the formal survival curves for non-treated patients, with formulae in solid boxes. Dotted lines show modification of original curves by treatment, with percentage of survival improvement in

dotted boxes.

In oppose to this wasteful practice of reduction of trophic cells during conventional treatment, we have preserved them by distraction from tumor in a favor of reparation of numerous sublethal injuring of normal cells aside of tumor, which induced by low, non-tumoricidal dose of total body irradiation [142] [187] [188], This approach called by us "the competitive therapy", bases on the natural property of circulating stem and progenitor cells originated from bone marrow, to take part in reparation-regeneration of injured cells in normal tissues [189] [190] [191] [192]. The matter of fundamental biological processes, well-known in radiobiology, is that slightly injured, but extremely excessive normal cells force an HSC to readdress their original priority onto a reparation of numerous sub-lethal damages, which threatens the health, being a genuine hazard. These properties of HSC do not take in account by oncoimmunologists for explanation of abscopal phenomenon [193] [194], which terminal matter is "an action at a distance from the treated volume". They are again assuming stimulation of anti-cancer immunity. Meanwhile, reparation -regeneration in the sub-lethally injured normal tissues of dogs (Table 1) are quite applicable to clinical conditions [188] [195] [196] [197].

Figure 10 illustrates the mechanism of "competitive" therapy without using of strong cytotoxic impact, which leads to lethal damages of HSC and extra-loss of CPR.

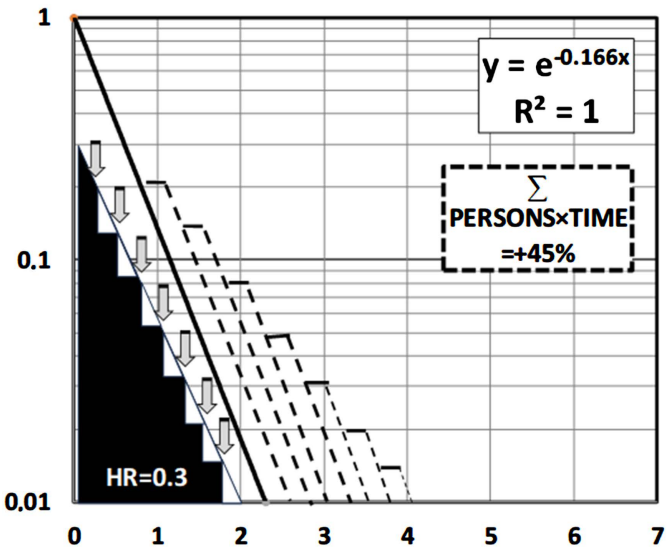

Figure 10. General schemes for effect of competitive treatment [141] [144] [182] [186] on hematopoiesis and survival of cancer patients with a very low HSC' proliferative resource (CPR), which does not permit to perform of conventional cytotoxic therapy. Abscissae: time, years. Ordinate: survival, relative units. Black area HR: current natural proliferative resource of hematopoietic system (CPR), as an integral of the number of active HSC by their Hayflick's limit, relative units. White areas show a consequence of redirection of morphogenic cells on reparation of numerous sublethal injuries of cells in the host s body. Gray arrows show the start of repeated low dose therapy (non-lethal for cells). Thick solid line presents the formal survival curve for non-treated patients (formulae is in solid framed box). Dotted lines show modification of original curve by treatment (percentage

of survival' improvement is in dotted boxes).

The advantage of application of competitive-abscopal therapy toward subjects with weakened hematopoiesis is based on **Table 1** [144], **Figure 5** [141], and [187]. The repeated distraction (pulling) of morpphogenic cells from tumor leads to the 3-years survival' benefit as high, as +45% in subjects with low dose total body irradiation, especially those, which have weak-low hematopoietic resource CPR (black area HR = 0.3 on **Figure 10**). Correspondently, this advantage is more probable in subjects with advanced cancer, and for the successful implementation of this approach, an accurate assessment of personal CPR is highly desirable. The graphical analysis on **Figure 10** is most applicable to the waist majority of cases with different grade of exhaustion of natural proliferative resource of hematopoietic system (CPR), manifested by lymphopenia $< 1 \times 10^9$ per l. They correspond to the incurable cancer with vessels net involution - necrosis in a primary tumor, and with uncontrolled spreading of the cancer. **Figure 11** illustrate kinetic aspects of this approach.

The treatment of tumor during quasi-exponential increasing its biomass is a rare case, because it is earliest stage of growth, which is unlimited by the delay in the corresponding capillary network development or lack of CPR (**Figure 11**, left side). The case of the earliest lack of CPR or capillary network in tumor (transition zone to quasi-linear malignant growth on **Figure 11**), corresponds to the trophic discomfort for some cancer cells and their trend to the loss of habitual residence (homing). These cases, both staying within I-II stages, N1, M0, used to be radically solved by surgery and do not relate here to **Figure 9** and **Figure 10**, which depict the advanced stages of cancer with widespread metastases, and corresponds to the right sight of **Figure 11**.

Importantly, even at identical original diagnoses TNM for two untreated subjects, a prognosis can be better as fare as individual CPR closer to the mean CPR value for the health population.

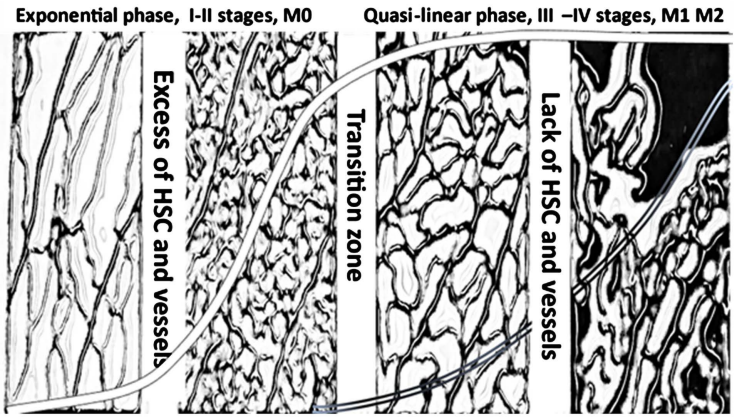

Figure 11. The proper relations between interconnected parameters of a primary tumor growth, metastases, and angiogenesis. Thick white line simulates development of a primary tumor' mass in terms of relatively short exponential, and prolonged quasi-linear phases of a growth. Thin white line simulates development of a distant metastases. The rectangular pictures are the microscope field of view for the blood vessels' density on the

microscopic slices; solid black area is a necrosis. (extracted from [131] [183] [198]).

The reason for that is a postponing of a conflict between the ability of tumor mass to continue an unlimited, exponential growth, and disability of current CPR to provide the creation of new extra-physiological vascular net needed for that. Thus, the longer local growth the primary tumor is, the lower the probability of tumor cells' emigration and spreading, which is equal to the postponing of distant metastasis on **Figure 10**. That is why, any deterioration of the trophic supply of the primary tumor during the therapy increases the probability of tumor cells emigration [199].

Ubiquitous ignoring this factor, when blood lymphocytes number $< 1 \times 10^9$ per l, is one of the reasons for overusing substantially the cytotocidal treatments that are more likely to harm than to benefit a patient [200] [201].

J. Uriel assumed rightly that we have very few chances of really cure cancer as long as we continue to treat malignancies with cell-killing therapies. He sees the tumor reversion, stem cell management and genomic analysis of embryo-fetal development, as appropriated candidates for future active research [202].

The existing of a narrow interval between lack of a treatment and an over-treatment of the host organism, which have a low level of CPR, persuades that only a moderate somatic harm is ultimately acceptable to get short-term CR or PR. In other words, the payment for therapeutic benefit is the spending of the rest of CPR, as a shagreen leather-Magic skin of the patient anyway. The "shagreen leather" is shrinking, because it spends CD133 stem endothelial progenitor cells promoted a tumor growth by supporting angiogenesis as well, as CD34, progenitor Treg promoted malignant growth also. The known perspective anti-tumor Tocilizumab lowers these mophogenic cells level [203] [204] together with the lowering of IL-6 [205] and T-cells at large [206], being true immuno-suppressant. The long-term and low-toxic total body therapy acts via abscopal mechanism [207], which is wrongly considered as "systemic immune response mediated by the stimulating effects of radiation on the immune system". The metronomic therapy (MT) proposed recently, consists of chronic administration of less toxic lower dosages of cytotoxic drugs with short or no drug-free breaks. Clinical experience of MT with different radiomimetic drugs (like Capecitabine, Fluorouracil (5FU), Cyclophosphamide) shows a lack of, or limited, host-response effects, which could maintain a stable state of disease. Alas, it was traditionally discussed again in one-sided terms of reduction in immunosuppression, or promotion of an immunostimulatory microenvironment [208] [209]. Actually, it is a paraphrasing of "competing" therapy justified by us, based on *redistribution* of limited CPR from tumor to reparable artificial injuries in normal cells of the host.

8. Overall Conclusion

The contradictory and insignificant practically, the dogma of antitumor cellular immunity, being only a narrow branch of lymphopoietic system functions, proved unable during many decades of the dominance to change the more than

modest criteria of survival at advanced cancer. It is wasteful to ignore the established basic knowledge regarding the critical role that circulating hematopoietic stem (HSC) and progenitor cells, as well as lymphopoiesis, play in preserving the viability of numerous human tissues under both physiological and pathological conditions, such as pregnancy, cancer, wound healing, grafts, and more. As a current proliferative resource (CPR) of HSC is limited individually by cells number and telomeres' length at the birth, its irreversible spending is equivalent to the shortening life span. But immunooncology confess post-therapeutic inactivation of stem-progenitors pool with concomitant lymphopenia, as annoying "complication". However, it is the main mechanism of temporal attenuation/damping of morphogenic activity of stem/progenitor cells-migrants in the tumor, as it has a privilege in consumption of CPR, being perceived by the host as a quasi-embryonic tissue. Underestimation of the treat of "complications" results in one-side strategy to get ultimately the tumor's "answer" to the therapy, neglecting a harm for general somatic wellbeing. This dramatic mistake impasses the developing of reasoned approaches aimed for preservation of residual CPR , *i.e.* life span, and to transformation of current treatments from double-edged sword to the saving the life. For protection of the patients, a demanding control of existing and prospective treatment regimens for myelotoxicity is necessary, as many of those diagnosed have deep pathognomonic CPR deficit already before treatment.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Ménétrier-Caux, Ray-Coquard, C.I., Blayand, J.-Y. and Caux, C. (2019) Lymphopenia in Cancer Patients and Its Effects on Response to Immunotherapy: An Opportunity for Combination with Cytokines? *Journal for ImmunoTherapy of Cancer*, **7**, Article No. 85. https://doi.org/10.1186/s40425-019-0549-5

[2] Cabanos, H.F. and Hata, A.N. (2021) Emerging Insights into Targeted Therapy-Tolerant Persister Cells in Cancer. *Cancers*, **13**, Article No. 2666. https://doi.org/10.3390/cancers13112666

[3] Side Effects of Targeted Therapy (2023) FORCE. https://www.facingourrisk.org

[4] Criscitiello, C., Metzger-Filho, O., Saini, K.S., de Castro Jr, G., Diaz, M., La Gerche A., *et al.* (2012) Targeted Therapies in Breast Cancer: Are Heart and Vessels Also Being Targeted? *Breast Cancer Research*, **14**, Article No. 209. https://doi.org/10.1186/bcr3142

[5] Burocchi, A., Colombo, M.P. and Piconese, S. (2013) Convergences and Divergences of Thymus- and Peripherally Derived Regulatory T Cells in Cancer. *Frontiers in Immunology*, **4**, Article No. 247. https://doi.org/10.3389/fimmu.2013.00247

[6] Mishra, S., Srinivasan, S., Ma, C. and Zhang, N. (2021) CD8+ Regulatory T Cell—A Mystery to Be Revealed. *Frontiers in Immunology*, **12**, Article ID: 708874. https://doi.org/10.3389/fimmu.2021.708874

[7] Wenbo, L. and Wang, J. (2017) Uncovering the Underlying Mechanism of Cancer Tumorigenesis and Development under an Immune Microenvironment from Global Quantification of the Landscape. *Journal of the Royal Society Interface*, **14**, Article ID: 20170105. https://doi.org/10.1098/rsif.2017.0105

[8] Chan Wah Hak, C.M.L., Rullan, A., Patin, E.C., Pedersen, M., Melcher, A.A. and Harring-ton, K.J. (2022) Enhancing Antitumour Innate Immunity by Targeting the DNA Damage Response and Pattern Recognition Receptors in Combination with Radio-Therapy. *Frontiers in Oncology*, **12**, Article ID: 971959. https://doi.org/10.3389/fonc.2022.971959

[9] Sakaguchi, S. (2005) Naturally Arising Foxp3-Expressing CD25+CD4+ Regulatory T Cells in Immunological Tolerance to Self and Non-Self. *Immunology*, **6**, 345-352. https://doi.org/10.1038/ni1178

[10] Ekka-Zochar, A., Zitser-Gurevich, Y., Mandel, M., Weiss-Salz, I., Nir Ba, S., Mor, E., *et al*. (2006) Graft Survival and Its Determinants: A 3 Year National Experience with Liver Transplantation in Israel. *The Israel Medical Association Journal*, **8**, 400-405.

[11] Harding, C., Pompei, F. and Wilson, R. (2012) Peak and Decline in Cancer Incidence, Mortality, and Prevalence at Old Ages. *Cancer*, **118**, 1371-1386. https://doi.org/10.1002/cncr.26376

[12] Heymoch, J., Folkman, J. and Kalluri, R. (2010) Tumor Angiogenesis. Cancer Medicine. 8th Edition, People's Medical Publishing House, Shelton, 148-169.

[13] De Palma, M., Biziato, D. and Petrova, T.V. (2017) Microenvironmental Regulation of Tumor Angiogenesis. *Nature Reviews Cancer*, **17**, 457-474. https://doi.org/10.1038/nrc.2017.51

[14] Kopjar, N., Garaj-Vrhovac, V., Kasuba, V., Rozgaj, R., Ramic, S., Pavlica, V., *et al*. (2009) Assessment of Genotoxic Risks in Croatian Health Care Workers Occupationally Exposed to Cytotoxic Drugs: A Multi-Biomarker Approach. *International Journal of Hygiene and Environmental Health*, **212**, 414-431. https://doi.org/10.1016/j.ijheh.2008.10.001

[15] Shuryak, I., Hahnfeldt, P., Hlatky, L., Suchs, R.K. and Brenner, D.J. (2009) A New View of Radiation Induced Cancer: Integrating Short- and Long-Term Processes. Part II: Second Cancer Risk Estimation. *Radiation and Environmental Biophysics*, **48**, 275-286. https://doi.org/10.1007/s00411-009-0231-2

[16] Common Terminology Criteria for Adverse Events (CTCAE)/Version 3.0 (2006) AMGEN Oncology. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

[17] Garau, M.M., Calduch, A.L. and López, E.C. (2011) Radiobiology of the Acute Radiation Syndrome. *Reports of Practical Oncology and Radiotherapy*, **16**, 123-130. https://doi.org/10.1016/j.rpor.2011.06.001

[18] Sanmamed, M.F. and Chen, L.A. (2018) Paradigm Shift in Cancer Immunotherapy: From Enhancement to Normalization. *Cell*, **175**, 313-326. https://doi.org/10.1016/j.cell.2018.09.035

[19] Manzo, G. (2019) Similarities between Embryo Development and Cancer Process Suggest New Strategies for Research and Therapy of Tumors: A New Point of View. *Frontiers in Cell and Developmental Biology*, **7**, Article No. 20. https://doi.org/10.3389/fcell.2019.00020

[20] Tyler, R.W.C. and Evereti, N.B.A. (1966) Radioautographic Study of Hemopoietic Repopulation Using Irradiated Parabiotic Rats Relation to the Stem Cell Problem.

Blood, **28**, 873-890. https://doi.org/10.1182/blood.V28.6.873.873

[21] Booth, C., Tudor, G., Tudor, J., Katz, B.P. and Mac Vittie, T.J. (2012) The Acute Gastrointestinal Syndrome in High-Dose Irradiated Mice. *Health Physics*, **103**, 383-399. https://doi.org/10.1097/HP.0b013e318266ee13

[22] Carroll, H.W. and Kimeldorf, D.J. (1967) Protection through Parabiosis against the Lethal Effects of Exposure to Large Doses of X-Rays. *Science*, **156**, 954-955. https://doi.org/10.1126/science.156.3777.954

[23] de Lucas, B., Perez, M. and Galvez, B.G. (2018) Importance and Regulation of Adult Stem Cell Migration. *Journal of Cellular and Molecular Medicine*, **22**, 746-754. https://doi.org/10.1111/jcmm.13422

[24] Greenberger, J.S. and Epperly, M. (2019) Bone Marrow-Derived Stem Cells and Radiation Response. *Seminars in Radiation Oncology*, **19**, 133-139. https://doi.org/10.1016/j.semradonc.2008.11.006

[25] Young, H.E., Hyer, L., Black Jr, A.C. and. Robinson Jr, J.S. (2014) Adult Stem Cells: From Bench-Top to Bedside. In: *Tissue Regeneration*: *Where Nanostructure Meets Biology*, Biotech, North Brunswick, 1-60. https://doi.org/10.1142/9789814494847_0001

[26] Young, H.E., Lochner, F., Lochner, D., Black, J.F., Coleman, J., Young, V.E., *et al.* (2017) Primitive Stem Cells in Adult Human Peripheral Blood. *Journal of Stem Cells & Regenerative Medicine*, **1**, 1-8. https://doi.org/10.33425/2639-9512.1008

[27] Carver, D.E. (2015) Pediatric Red Marrow and Organ Radiation Dose Estimates in Computed Tomography from Monte Carlo Simulations. Ph.D. Dissertation, Vanderbilt University, Nashville.

[28] Porada, C.D., Atala, A.J. and Almeida-Porada, G. (2016) The Hematopoietic System in the Context of Regenerative Medicine. *Methods*, **99**, 44-61. https://doi.org/10.1016/j.ymeth.2015.08.015

[29] Sieburg, H.B., Cattarossi, G. and Muller-Sieburg, C.E. (2013) Lifespan Differences in Hematopoietic Stem Cells Are Due to Imperfect Repair and Unstable Mean-Reversion. *PLOS Computational Biology*, **9**, e1003006. https://doi.org/10.1371/journal.pcbi.1003006

[30] Krueger, A. (2018) Thymus Colonization: Who, How, How Many? *Archivum Immunologiae et Therapiae Experimentalis* (*Warsz*), **66**, 81-88. https://doi.org/10.1007/s00005-017-0503-5

[31] Araki, T., Nishino, M., Gao, W., Dupuis, J., Hunninghake, G.M., Murakami, T., *et al.* (2016) Normal Thymus in Adults: Appearance on CT and Associations with Age, Sex, BMI and Smoking. *European Radiology*, **26**, 15-24. https://doi.org/10.1007/s00330-015-3796-y

[32] Lazzer, S., Bedogni, G., Lafortuna, C.L., Marazzi, N., Busti, C., Galli, R., *et al.* (2010) Relationship between Basal Metabolic Rate, Gender, Age, and Body Composition in 8780 White Obese Subjects. *Obesity*, **18**, 71-78. https://doi.org/10.1038/oby.2009.162

[33] Evetts, A.-A.M. (2016) Body and Organ Measurements in Infants and Neonates: An Autopsy Study. Electronic Thesis and Dissertation Repository, The University of Western Ontario, London, 3989. https://ir.lib.uwo.ca/etd/3989

[34] Kendall, M.D., Johnson, H.R.M. and Singh, J. (1980) The Weight of the Human Thymus Gland at Necropsy. *Journal of Anatomy*, **131**, 485-499.

[35] Height, Weight and Body Mass Indext of the Population. (2021) Statistisches Bundesamt.

https://www.destatis.de/EN/Themes/Society-Environment/Health/Health-Status-Behaviour-Relevant-Health/Tables/body-mass-index-total.html

[36] Yan, J., Greer, J.M., Hull, R., O'Sullivan, J.D., Henderson, D., Read, S.J., *et al.* (2010) The Effect of Ageing on Human Lymphocyte Subsets: Comparison of Males and Females. *Immunity & Ageing*, **7**, Article No. 4. http://www.immunityageing.com/content/7/1/4 https://doi.org/10.1186/1742-4933-7-4

[37] Werner, B., Beier, F., Hummel, S., Balabanov, S., Lassay, L., Orlikowsky, T., *et al.* (2015) Reconstructing the *in Vivo* Dynamics of Hematopoietic Stem Cells from Telomere Length Distributions. *eLife*, **4**, e08687. https://doi.org/10.7554/eLife.08687

[38] Liu, P., Jiang, H., Che, M., Fu, R., Wang, H., Li, L., *et al.* (2018) Abnormal CD25 Expression on Hematopoietic Cells in Myelodysplastic Syndromes. *Leukemia Research*, **67**, 12-16. https://doi.org/10.1016/j.leukres.2017.11.010

[39] Douaisi, M., Resop, R.L.S., Nagasawa, M., Craft, J., Jamieson, B.D., Blom, B., *et al.* (2017) CD31, a Valuable Marker to Identify Early and Late Stages of T Cell Differentiation in the Human Thymus. *The Journal of Immunology*, **198**, 2310-2319. https://doi.org/10.4049/jimmunol.1500350

[40] Abdellatif, H. and Shiha, G. (2018) PD-L1 Expression on Circulating CD34+ Hematopoietic Stem Cells Closely Correlated with T-Cell Apoptosis in Chronic Hepatitis C Infected Patients. *International Journal of Stem Cells*, **11**, 78-86. https://doi.org/10.15283/ijsc17047

[41] Case, J., Mead, L.E., Bessler, W.K., Prater, D., White, H.A., Reza Saadatzadeh, M., *et al.* (2007) Human CD34+AC133+VEGFR-2+ Cells Are Not Endothelial Progenitor Cells but Distinct, Primitive Hematopoietic Progenitors. *Experimental Hematology*, **35**, 1109-1118. https://doi.org/10.1016/j.exphem.2007.04.002

[42] Saran, N., Pommerencke, J., Witzlau, K., Regelin, M. and Krueger, A. (2012) Extra-Thymic Physiological T Lineage Progenitor Activity Is Exclusively Confined to Cells Expressing either CD127, CD90, or High Levels of CD117. *PLOS ONE*, **7**, e30864. https://doi.org/10.1371/journal.pone.0030864

[43] Ghaedi, M., Steer, C.A., Martinez-Gonzalez, I., Halim, T.Y.F., Abraham, N. and Takei, F. (2016) Common-Lymphoid-Progenitor-Independent Pathways of Innate and T Lymphocyte Development. *Cell Reports*, **15**, 471-480. https://doi.org/10.1016/j.celrep.2016.03.039

[44] Benz, C., Copley, L.R., Kent, D., Woehrer, S., Rowe, K. and Eaves, C.J. (2010) The Reduced Lymphopoietic Potential of a Novel Subclass of Hematopoietic Stem Cells Is Mediated by Specific Defects in the Production and Activity of Their Common Lymphoid Progenitor (CLP) Progeny. *Blood*, **116**, 576. https://doi.org/10.1182/blood.V116.21.576.576

[45] Yang, L., Bryder, D., Adolfsson, J., Nygren, J., Månsson, R., Sigvardsson, M., *et al.* (2005) Identification of Lin-Sca1+kit+CD34+Flt3- Short-Term Hematopoietic Stem Cells Capable of Rapidly Reconstituting and Rescuing Myeloablated Transplant Recipients. *Blood*, **105**, 2717-2723. https://doi.org/10.1182/blood-2004-06-2159

[46] Shoutko, A., Ekimova, L., Mus, V. and Sokurenko, V. (2012) Fluctuations of CD34+ Cells Number in Blood of Cancer Patients during Final Year of Life. *Medical and Health Science Journal*, **13**, 7-13.

[47] Shoutko, A.N., Gerasimova, O.A., Ekimova, L.P., Zherebtsov, F.K., Mus, V.F., Matyurin, K.S., *et al.* (2017) Lymphocyte Reproductive Activity Normalized to Numbers of Hematopoietic Stem Cells in Blood and Rate of Death in Fatal Diseases. *International Journal of Genetics and Genomics*, **5**, 54-62.

https://doi.org/10.11648/j.ijgg.20170505.12

[48] Shoutko, A.N., Mus, V.F. and Maystrenko, D.N. (2020) Chapter 13. Peripheral Signs of Lymphocytopoiesis in the Prediction of the Terminal Life Span of Cancer Patients. In: Murdaka, G., Ed., *Current Topics in Medicine and Medical Research*, Book Publisher International, London, 138-154.

[49] Fliedner, T.M. and Graessle, D.H. (2008) Hematopoietic Cell Renewal Systems: Mechanisms of Coping and Failing after Chronic Exposure to Ionizing Radiation. *Radiation and Environmental Biophysics*, **47**, 63-69. https://doi.org/10.1007/s00411-007-0148-6

[50] Holtan, S.G., Creedon, D.J., Haluska, P. and Markovic, S.N. (2009) Cancer and Pregnancy: Parallels in Growth, Invasion, and Immune Modulation and Implications for Cancer Therapeutic Agents. *Mayo Clinic Proceedings*, **84**, 985-1000. https://doi.org/10.1016/S0025-6196(11)60669-1

[51] Costanzo, V., Bardelli, A., Siena, S. and Abrignani, S. (2018) Exploring the Links between Cancer and Placenta Development. *Open Biology*, **8**, Article ID: 180081. https://doi.org/10.1098/rsob.180081

[52] Ho, K.Y.L., Carr, R.L., Dvoskin, A.D. and Tanentzapf, G. (2023) Kinetics of Blood Cell Differentiation during Hematopoiesis Revealed by Quantitative Long-Term Live Imaging. *eLife*, **12**, e84085. https://doi.org/10.7554/eLife.84085.sa2

[53] Shoutko, A. (2021) The Possible Involvement of Apoptotic Decay of Terminal Deoxynucleotidyl Transferase-Positive Lymphocytes in the Reutilization of the Extracellular DNA Fragments by Surrounding Living Cells. *Open Journal of Biophysics*, **11**, 371-382. https://doi.org/10.4236/ojbiphy.2021.114014

[54] Kast, R.E. (2022) High Neutrophil-to-Lymphocyte Ratio Facilitates Cancer Growth—Currently Marketed Drugs Tadalafil, Isotretinoin, Colchicine, and Omega-3 to Reduce It: The TICO Regimen. *Cancers*, **14**, Article No. 4965. https://doi.org/10.3390/cancers14194965

[55] Verma, N.K., Wong, B.H.S., Poh, Z.S., Udayakumar, A., Verma, R. and Goh, R. (2022) Obstacles for T-Lymphocytes in the Tumour Microenvironment: Therapeutic Challenges, Advances and Opportunities beyond Immune Checkpoint. *EBioMedicine*, **83**, Article ID: 104216. https://doi.org/10.1016/j.ebiom.2022.104216

[56] Yuan, X., Rasul, F., Nashan, B. and Sun, C. (2021) Innate Lymphoid Cells and Cancer: Role in Tumor Progression and Inhibition. *European Journal of Immunology*, **51**, 2188-2205. https://doi.org/10.1002/eji.202049033

[57] Pido-Lopez, J., Imami, N. and Aspinall, R. (2001) Both Age and Gender Affect Thymic Output: More Recent Thymic Migrants in Females than Males as They Age. *Clinical and Experimental Immunology*, **125**, 409-413. https://doi.org/10.1046/j.1365-2249.2001.01640.x

[58] Le, J., Ha, V.L., Li, F., Camacho, V., Patel, S., Welner, R.S., *et al.* (2019) Single Cell Transcriptome Mapping of Human Thymopoiesis Reveals a Continuum of Cell States during T-Lineage Specification and Commitment. *Blood*, **134**, 1183. https://doi.org/10.1182/blood-2019-129886

[59] Leposavic, G., Pesic, V., Kosec, D., Radojevic, K., Arsenovic-Ranin, N., Pilipovic, I., *et al.* (2006) Age-Associated Changes in CD90 Expression on Thymocytes and in TCR-Dependent Stages of Thymocyte Maturation in Male Rats. *Experimental Gerontology*, **41**, 574-589. https://doi.org/10.1016/j.exger.2006.03.006

[60] Ginaldi, L., Farahat, N., Matutes, E., De Martinis, M., Morilla, R. and Catovsky, D. (1996) Differential Expression of T Cell Antigens in Normal Peripheral Blood Lymphocytes: A Quantitative Analysis by Flow Cytometry. *Clinical Pathology*, **49**,

539-544. https://doi.org/10.1136/jcp.49.7.539

[61] Lee, R.W.J., Creed, T.J., Schewitz, L.P., Newcomb, P.V., Nicholson, L.B., Dick, A.D., *et al.* (2007) Dayan CD4+CD25int T Cells in Inflammatory Diseases Refractory to Treatment with Glucocorticoids. *The Journal of Immunology*, **179**, 7941-7948. https://doi.org/10.4049/jimmunol.179.11.7941

[62] Ziegler, H., Welker, C., Sterk, M., Haarer, J., Rammensee, H.-G., Handgretinger, R., *et al.* (2014) Human Peripheral CD4+ Vδ1+ $\gamma\delta$T Cells Can Develop into $\alpha\beta$T Cells. *Frontiers in Immunology*, **5**, Article No. 645. https://doi.org/10.3389/fimmu.2014.00645

[63] Muro, R., Takayanagi, H. and Nitta, T. (2019) T Cell Receptor Signaling for $\gamma\delta$T Cell Development. *Inflammation and Regeneration*, **39**, Article No. 6. https://doi.org/10.1186/s41232-019-0095-z

[64] Demanelis, K., Jasmine, F., Chen, L.S., Chernoff, M., Tong, L., Delgado, D., *et al.* (2020) Determinants of Telomere Length across Human Tissues. *Science*, **369**, eaaz6876. https://doi.org/10.1126/science.aaz6876

[65] Mitchell, E., Chapman, M.S., Williams, N., Dawson, K.J., Mende, N. and Calderbank, E.F. (2022) Clonal Dynamics of Haematopoiesis across the Human Lifespan. *Nature*, **606**, 343-350. https://doi.org/10.1038/s41586-022-04786-y

[66] Vaiserman, A. and Krasnienkov, D. (2020) Telomere Length as a Marker of Biological Age: State-of-the-Art, Open Issues, and Future Perspectives. *Frontiers in Genetics*, **11**, Article ID: 630186. https://doi.org/10.3389/fgene.2020.630186

[67] Wu, X., Zhu, H., Xu, Y., Kong, B. and Tan, Q. (2023) Chronic Wounds: Pathological Characteristics and Their Stem Cell-Based Therapies. *Engineered Regeneration*, **4**, 81-94. https://doi.org/10.1016/j.engreg.2022.11.004

[68] Danielyan, L., Schwab, M., Siegel, G., Brawek, B., Garaschuk, O., Asavapanumas, N., *et al.* (2020) Cell Motility and Migration as Determinants of Stem Cell Efficacy. *EBioMedicine*, **60**, Article ID: 102989. https://doi.org/10.1016/j.ebiom.2020.102989

[69] Lee, J.Y. and Hong, S.-H. (2020) Hematopoietic Stem Cells and Their Roles in Tissue Regeneration. *International Journal of Stem Cells*, **13**, 1-12. https://doi.org/10.15283/ijsc19127

[70] Zhang, Y.T., He, K.J., Zhang, J.B., Ma, Q.-H., Wang, F. and Liu, C.-F. (2021) Advances in Intranasal Application of Stem Cells in the Treatment of Central Nervous System Diseases. *Stem Cell Research & Therapy*, **12**, Article No. 210. https://doi.org/10.1186/s13287-021-02274-0

[71] Olnes, M.J., Kotliarov, Y., Biancotto, A., Cheung, F., Chen, J., Shi, R., *et al.* (2016) Effects of Systemically Administered Hydrocortisone on the Human Immunome. *Scientific Reports*, **6**, Article No. 23002. https://doi.org/10.1038/srep23002

[72] Sheu, T.-T. and Chiang, B.-L. (2021) Lymphopenia, Lymphopenia-Induced Proliferation, and Autoimmunity. *International Journal of Molecular Sciences*, **22**, Article No. 4152. https://doi.org/10.3390/ijms22084152

[73] Ahmed, A.S.I., Sheng, M.H.C., Wasnik, S., Baylink, D.J. and Lau, K.H.W. (2017) Effect of Aging on Stem Cells. *World Journal of Experimental Medicine*, **7**, 1-10. https://doi.org/10.5493/wjem.v7.i1.1

[74] IAEA and WHO Modul YIII-b. Biological Effects of Ionizing Radiation on Tissues, Organs and Systems. https://www-pub.iaea.org>epmedt>Day_2

[75] Dörr, H. and Meineke, V. (2011) Acute Radiation Syndrome Caused by Accidental Radiation Exposure—Therapeutic Principles. *BMCMedicine*, **9**, Article No. 126. http://www.biomedcentral.com/1741-7015/9/126 https://doi.org/10.1186/1741-7015-9-126

[76] Deli, G. (2022) Mechanism of Action and Use of Radiomimetic Compounds. *Hadmérnök*, **17**, 101-115. https://doi.org/10.32567/hm.2022.1.7

[77] Gourd, N.M. and Nikitas, N. (2020) Multiple Organ Dysfunction Syndrome. *Journal of Intensive Care Medicine*, **35**, 1564-1575. https://doi.org/10.1177/0885066619871452

[78] Richardson, R.B. (2009) Ionizing Radiation and Aging: Rejuvenating an Old Idea. *Aging* (*Albany NY*), **1**, 887-902. https://doi.org/10.18632/aging.100081

[79] Meunier, N., Beattie, J.H., Ciarapica, D., O'Connor, J.M. and Andriollo-Sanchez, M. (2005) Basal Metabolic Rate and Thyroid Hormones of Late Middle-Aged and Older Human Subjects: The ZENITH Study. *European Journal of Clinical Nutrition*, **59**, S53-S57. https://doi.org/10.1038/sj.ejcn.1602299

[80] Shoutko, A.N., Ekimova, L.P., Vasilyeva, M.J. and Shatinina, N.N. (2000) Tissue Factors Involved in Cancer Induction. *Proceedings of the* 5*th International Conference on High Level of Natural Radiation and Radon Areas*: *Radiation Dose and Health Effects*, Munich, 4-7 September 2000, 467-470. https://www.researchgate.net/publication/337672950

[81] Szadvari, I., Krizanova, O. and Babula, P. (2016) Athymic Nude Mice as an Experimental Model for Cancer Treatment. *Physiological Research*, **65**, S441-S453. https://doi.org/10.33549/physiolres.933526

[82] Sharkey, F.E. and Fogh, J. (1979) Incidence and Pathological Features of Spontaneous Tumors in Athymic Nude Mice. *Cancer Research*, **39**, 833-839.

[83] Stutman, O. (1979) Spontaneous Tumors in Nude Mice: Effect of the Viable Yellow Gene. *Experimental Cell Biology*, **47**, 129-135. https://doi.org/10.1159/000162929

[84] Moyer, A.M., Yu, J., Sinnwell, J.P., Dockter, T.J., Suman, V.J., Weinshilboum, R.M., *et al.* (2019) Spontaneous Murine Tumors in the Development of Patient Derived Xenografts: A Potential Pitfall. *Oncotarget*, **10**, 3924-3930. https://doi.org/10.18632/oncotarget.27001

[85] Puchalapalli, M., Zeng, X., Mu, L., Anderson, A., Hix Glickman, L., Zhang, M., *et al.* (2016) NSG Mice Provide a Better Spontaneous Model of Breast Cancer Metastasis than Athymic (Nude) Mice. *PLOS ONE*, **11**, e0163521. https://doi.org/10.1371/journal.pone.0163521

[86] https://insights.envigo.com/hubfs/R746%20R2G2%20Technical%20Resources/Development%20and%20characterization%20of%20the%20ultra%20immunodeficient%20R2G2%20mouse%20model.pdf

[87] Lakshmi, P.S., Oduor, C.I., Forconi, C.S., M'Bana, V., Bly, C., Gerstein, R.M., *et al.* (2023) Endemic Burkitt Lymphoma Avatar Mouse Models for Exploring Inter-Patient Tumor Variation and Testing Targeted Therapies. *Life Science Alliance*, **6**, e202101355. https://doi.org/10.26508/lsa.202101355

[88] Britt, N.M., Miller, M.K., Hoover, D.B. and Schweitzer, J.B. (2018) Immunodeficient R2G2 Mouse Strain Yields Spleens with Unusual Cytoarchitecture and Sympathetic Innervation. Appalachian Student Research Forum. 205. East Tennessee State University.

[89] Huang, H. and Cantor, A.B. (2010) Common Features of Megakaryocytes and Hematopoietic Stem Cells: What's the Connection? *Journal of Cellular Biochemistry*, **107**, 857-864. https://doi.org/10.1002/jcb.22184

[90] The Human Protein Atlas. Sections: Tissue Cell Type. https://www.proteinatlas.org/about/lisence#citation-guidelines_for_the_human_protein_atlas

[91] Kim, Y.E., Calderon, A.A., Favaro, P., Glass, D.R., Tsai, A.G., Borges, L., *et al.* (2022) Expression of Terminal Deoxynucleotidyl Transferase (TdT) Identifies Lymphoid-Primed Progenitors in Human Bone Marrow. https://doi.org/10.1101/2022.10.30.514380

[92] Janossy, G. and Pizzolo, G. (1979) Lymphocytes. 2. Differentiation. Differentiation of Lymphoid Precursor Cells. *Journal of Clinical Pathology*, **13**, 48-58. https://doi.org/10.1136/jcp.s3-13.1.48

[93] Liu, B., Qu, J., Zhang, W., Belmonte, J.C.I. and Liu, G.-H. (2022) A Stem Cell Aging Framework, from Mechanisms to Interventions. *Cell Reports*, **41**, Article ID: 111451. https://doi.org/10.1016/j.celrep.2022.111451

[94] Mackay, L.S., Dodd, S., Dougall, I.G., Tomlinson, W., Lordan, J., Fisher, A.J., *et al.* (2013) Isolation and Characterisation of Human Pulmonary Microvascular Endothelial Cells from Patients with Severe Emphysema. *Respiratory Research*, **14**, 1-11. https://doi.org/10.1186/1465-9921-14-23 https://pubmed.ncbi.nlm.nih.gov/23425195/

[95] Kakavoulia, M.-A. (2021) Overview of Very Small Embryonic like Stem Cells (VSELs) and Their Therapeutic Potential. *Aristotle Biomedical Journal*, **3**, 1-12.

[96] Ma, Y., Zhang, P., Wang F., Yang, J., Yang, Z. and Qin, H. (2010) The Relationship between Early Embryo Development and Tumourigenesis. *Journal of Cellular and Molecular Medicine*, **14**, 2697-2701. https://doi.org/10.1111/j.1582-4934.2010.01191.x

[97] Al-Deghaither, S.Y. (2015) Impact of Maternal and Neonatal Factors on Parameters of Hematopoietic Potential in Umbilical Cord Blood. *Saudi Medical Journal*, **36**, 704-712. https://doi.org/10.15537/smj.2015.6.11247

[98] Keshavarz, E., Sheikhyusefi, M.R., Pouya, E.K., Mirzamoradi, M., Khazaei, M., Moharamzad, Y., *et al.* (2021) Association between Fetal Thymus Size and Intrauterine Growth Restriction. *Journal of Diagnostic Medical Sonography*, **38**, 120-126. https://doi.org/10.1177/87564793211054747

[99] Wells, J.C.K., Davies, P.S.W., Fewtrell, M.S. and Cole, T.J. (2020) Body Composition Reference Charts for UK Infants and Children Aged 6 Weeks to 5 Years Based on Measurement of Total Body Water by Isotope Dilution. *European Journal of Clinical Nutrition*, **74**, 141-148. https://doi.org/10.1038/s41430-019-0409-x

[100] Ye, P. and Kirschner, D.E. (2002) Reevaluation of T Cell Receptor Excision Circles as a Measure of Human Recent Thymic Emigrants. *The Journal of Immunology*, **168**, 4968-4979. https://doi.org/10.4049/jimmunol.168.10.4968

[101] Joish, U.K., Rathod, T. and Anitha, P.S. (2022) Sonographic Estimated Fetal Weight within an Indian Cohort: Is the Hadlock Four Regression Model Appropriate or Does It Merit Adjustments? *The Journal of Diagnostic Medical Sonography*, **38**, 137-145. https://doi.org/10.1177/87564793211046603

[102] Yekeler, E., Tambag, A., Tunaci, A., Genchellac, H., Dursun, M., Gokcay, G., *et al.* (2004) Analysis of the Thymus in 151 Healthy Infants from 0 to 2 Years of Age. *Journal of Ultrasound in Medicine*, **23**, 1321-1326. https://doi.org/10.7863/jum.2004.23.10.1321

[103] Peng, Y.G., Yan, R.H., Song, W.Q., Peng, X.X. and Ni, X. (2020) Age-Dependent Changes of Total and Differential White Blood Cell Counts in Children. *Chinese Medical Journal*, **133**, 1900-1907. https://doi.org/10.1097/CM9.0000000000000854

[104] Kulmann-Leal, B., Ellwanger, J.H. and Chies, J.A.B. (2020) A Functional Interaction between the CCR5 and CD34 Molecules Expressed in Hematopoietic Cells Can Support (or Even Promote) the Development of Cancer. *Hematology, Transfusion*

and Cell Therapy, **42**, 70-76. https://doi.org/10.1016/j.htct.2019.10.001

[105] El-Helw, M., Chelvarajan, L., Abo-Aly, M., Soliman, M., Milburn, G., Congeret, A.L., *et al.* (2020) Identification of Human Very Small Embryonic like Stem Cells (VSELS) in Human Heart Tissue among Young and Old Individuals. *Stem Cell Reviews and Reports*, **16**, 181-185. https://doi.org/10.1007/s12015-019-09923-1

[106] Hénon, P., Kowalczyk, M., Aries, A., Vignon, C., Trébuchet, G. and Lahlil, R. (2022) Industrialized GMP Production of CD34+ Cells (ProtheraCytes®) at Clinical Scale for Treatment of Ischemic Cardiac Diseases Is Feasible and Safe. *Stem Cell Reviews and Reports*, **18**, 1614-1626. https://doi.org/10.1007/s12015-022-10373-5

[107] Wolfien, M., Klatt, D., Salybekov, A.A., Ii, M., Komatsu-Horii, M., Gaebel, R., *et al.* (2020) Hematopoietic Stem-Cell Senescence and Myocardial Repair-Coronary Artery Disease Genotype/Phenotype Analysis of Post-MI Myocardial Regeneration Response Induced by CABG/CD133+ Bone Marrow Hematopoietic Stem Cell Treatment in RCT PERFECT Phase 3. *EBioMedicine*, **57**, Article ID: 102862. https://doi.org/10.1016/j.ebiom.2020.102862

[108] Hashemi, G., Dight, J., Khosrotehrani, K. and Sormani, L. (2022) Melanoma Tumour Vascularization and Tissue-Resident Endothelial Progenitor Cells. *Cancers*, **14**, Article No. 4216. https://doi.org/10.3390/cancers14174216

[109] Dhumale, P., Nielsen, J.V., Hansen, A.C.S., Burton, M., Beck, H.C., Jørgensen, M.G., *et al.* (2023) CD31 Defines a Subpopulation of Human Adipose-Derived Regenerative Cells with Potent Angiogenic Effects. *Scientific Reports*, **13**, Article No. 14401. https://doi.org/10.1038/s41598-023-41535-1

[110] Maltby, S., Freeman, S., Gold, M.J., Baker, J.H.E., Minchinton, A.I., Gold, M.R., *et al.* (2011) Opposing Roles for CD34 in B16 Melanoma Tumor Growth Alter Early Stage Vasculature and Late Stage Immune Cell Infiltration. *PLOS ONE*, **6**, e18160. https://doi.org/10.1371/journal.pone.0018160

[111] Shoutko, A.N. (2022) Lymphopenia—What Is under the Term. *Hematology and Medical Oncology*, **7**, 1-2. https://doi.org/10.15761/HMO.1000236

[112] Saavedra, D., Añé-Kourí, A.L., Barzilai, N., Caruso, A., Cho, K.-H., Fontana, L., *et al.* (2023) Aging and Chronic Inflammation: Highlights from a Multidisciplinary Workshop. *Immunity & Ageing*, **20**, 25. https://doi.org/10.1186/s12979-023-00352-w

[113] Vanhoutte, G., van de Wiel, M., Wouters, K., Sels, M., Bartolomeeussen, L. and DeKeersmaecker, S. (2016) Cachexia in Cancer: What Is in the Definition? *BMJ Open Gastroenterology*, **3**, e000097. https://doi.org/10.1136/bmjgast-2016-000097

[114] Ritter, B. and Greten, F.R. (2019) Modulating Inflammation for Cancer Therapy. *Journal of Experimental Medicine*, **216**, 1234-1243. https://doi.org/10.1084/jem.20181739

[115] Liu, F., Li, L., Lan, M., Zou, Z., Kong, T., Cai, T., *et al.* (2021) Key Factor Regulating Inflammatory Microenvironment, Metastasis, and Resistance in Breast Cancer: Interleukin-1 Signaling. *Mediators of Inflammation*, **2021**, Article ID: 7785890. https://doi.org/10.1155/2021/7785890

[116] Boopathi, E. and Thangavel, C. (2021) Dark Side of Cancer Therapy: Cancer Treatment-Induced Cardiopulmonary Inflammation, Fibrosis, and Immune Modulation. *International Journal of Molecular Sciences*, **22**, Article No. 10126. https://doi.org/10.3390/ijms221810126

[117] Dimitriadis, E., Rolnik, D.L., Zhou, W., Estrada-Gutierrez, G., Koga, K., Francisco, R.P.V., *et al.* (2023) Pre-Eclampsia. *Nature Reviews Disease Primers*, **9**, Article No. 8. https://doi.org/10.1038/s41572-023-00417-6

[118] Cornelius, D.C., Cottrell, J.M., Amaral, L. and LaMarca, B. (2019) Inflammatory Mediators: A Causal Link to Hypertension during Preeclampsia. *British Journal of Pharmacology*, **176**, 1914-1921. https://doi.org/10.1111/bph.14466

[119] Rabiu, K.A., Adewunmi, A.A.A., Ottun, T., Akinlusi, F.M., Adebanjo, A.A. and Alausa, T.G. (2018) Risk Factors for Maternal Mortality Associated with Eclampsia Presenting at a Nigerian Tertiary Hospital. *International Journal of Women's Health*, **10**, 715-721. https://doi.org/10.2147/IJWH.S178729

[120] Rad, A. and Häggström, M. (2009) File: Hematopoiesis (Human) Diagram.

[121] Jimenez-Rodriguez, R.M., Patil, S., Keshinro, A., Shia, J., Vakiani, E. and Stadler, Z. (2020) Quantitative Assessment of Tumor-Infiltrating Lymphocytes in Mismatch Repair Proficient Colon Cancer. *OncoImmunology*, **9**, Article ID: 1841948. https://doi.org/10.1080/2162402X.2020.1841948

[122] Schlüter, A., Weller, P., Kanaan, O., Nel, I., Heusgen, L., Höing, B., *et al.* (2018) CD31 and VEGF Are Prognostic Biomarkers in Early-Stage, but Not in Late-Stage, Laryngeal Squamous Cell Carcinoma. *BMC Cancer*, **18**, Article No. 272. https://doi.org/10.1186/s12885-018-4180-5

[123] Inamoto, Y. and Lee, S.J. (2017) Late Effects of Blood and Marrow Transplantation. *Haematologica*, **102**, 614-625. https://doi.org/10.3324/haematol.2016.150250

[124] Zhao, J., Huang, W., Wu, Y., Luo, Y., Wu, B., Cheng, J., *et al.* (2020) Prognostic Role of Pretreatment Blood Lymphocyte Count in Patients with Solid Tumors: A Systematic Review and Meta Analysis. *Cancer Cell International*, **20**, Article No. 15. https://doi.org/10.1186/s12935-020-1094-5

[125] Serizawa, K., Tanaka, H., Morita, Y., Taniguchi, T., Ashida, T. and Matsumura, I. (2018) Immunemodulatory Effects of 5-Azacitidin through Expansion of Functional Regulatory T Cells on Paraneoplastic Inflammation Associated with Myelodysplastic Syndromes: A Case Report. *Frontiers in Oncology*, **8**, Article No. 2018. https://doi.org/10.3389/fonc.2018.00204

[126] Shoutko, A.N. (2019) Immunity or Morphogenesis in Cancer Development and Treatment. *Integrative Cancer Science and Therapeutics*, **6**, 1-8. https://doi.org/10.15761/ICST.1000317

[127] Sidney, L.E., Branch, M.J., Dunphy, S.E., Dua, H.S. and Hopkinson, A. (2014) Concise Review: Evidence for CD34 as a Common Marker for Diverse Progenitors. *Stem Cells*, **32**, 1380-1389. https://doi.org/10.1002/stem.1661

[128] Shoutko, A. (2019) Overview of Hematopoietic Stem Cells in Systemic Cancer Treatment, Aging, Pregnancy, and Radiation Hormesis. *Advances in Molecular Imaging*, **9**, Article No. 19. https://doi.org/10.4236/ami.2019.92003

[129] Hoang, D.M., Pham, P.T., Bach, T.Q., Ngo, A.T.L., Nguyen, Q.T. and Phan, T.T.K. (2022) Stem Cell-Based Therapy for Human Diseases. *Signal Transduction and Targeted Therapy*, **7**, Article No. 272. https://doi.org/10.1038/s41392-022-01134-4

[130] Young, M.R., Petruzzelli, G.J., Kolesiak, K., Achille, N., Lathers, D.M.R. and Gabrilovich, D.I. (2001) Human Squamous Cell Carcinomas of the Head and Neck Chemoattract Immune Suppressive CD34+ Progenitor Cells. *Human Immunology*, **62**, 332-341. https://doi.org/10.1016/S0198-8859(01)00222-1

[131] Shoutko, A.N. (2022) Tissues Protein Microenvironment and Survival by Age at Cancers. *Acta Scientific Cancer Biology*, **6**, Article No. 7.

[132] Shoutko, A.N. (2023) The Levels of CD34 and CD31 Markers in Normal Organs Determine the Survival Rate in Case of Their Malignization. *Diagnostic Radiology and Radiotherapy*, **14**, 153-154. http://radiag.bmoc-spb.ru/jour

[133] Shahriyari, L. and Komarova, N.L. (2013) Symmetric vs. Asymmetric Stem Cell Divisions: An Adaptation against Cancer? *PLOS ONE*, **8**, e76195. https://doi.org/10.1371/journal.pone.0076195

[134] Shoutko, A.N., Ekimova, L.P., Sokurenko, V.P., Matyurin, K.S. and Karamullin, M.A. (2011) Alternative Changes of Lymphopoiesis of Cancer Patients Are Retained during Radiation Therapy. *Proceedings of* 14*th International Congress of Radiation Research*, Varszaw, 28 August-1 September 2011, 163.

[135] Park, J., Lee, S.H., Gwak, M.S., Ko, J.S., Han, S., Choi, G.S., *et al.* (2021) Association between Neutrophil-Lymphocyte Ratio Change during Living Donor Liver Transplantation and Graft Survival. *Scientific Reports*, **11**, Article No. 4199. https://doi.org/10.1038/s41598-021-83814-9

[136] Semina, O.V., Semenets, T.N., Zamulaeva, I.A., Selivanova, E.I., Ilíina, T.P., Malyutina, Ya.V., *et al.* (2007) Thymodepressin Inhibits Migration of CD34+ Cells from Bone Marrow in Normal and Granulocyte CSF-Stimulated Hemopoiesis. *Bulletin of Experimental Biology and Medicine*, **144**, 831-834. https://doi.org/10.1007/s10517-007-0442-y

[137] Aykan, N.F. and Özatlı, T. (2020) Objective Response Rate Assessment in Oncology: Current Situation and Future Expectations. *World Journal of Clinical Oncology*, **11**, 53-73. https://doi.org/10.5306/wjco.v11.i2.53

[138] Retsky, M., Demicheli, R., Hrushesky, W., Baum, M. and Gukas, I. (2010) Surgery Triggers Outgrowth of Latent Distant Disease in Breast Cancer: An Inconvenient Truth? *Cancers*, **2**, 305-337. https://doi.org/10.3390/cancers2020305

[139] Shoutko, A.N. (2019) Immunity or Morphogenesis in Cancer Development and Treatment Integrative Cancer Science and Therapeutics. *Integrative Cancer Science and Therapeutics*, **6**, 1-8. https://doi.org/10.15761/ICST.1000317

[140] Shoutko, A.N. (2020) Cancer Uses the Common Morphogenesis Source of the Host. *Open Journal of Biophysics*, **10**, 175-190. https://doi.org/10.4236/ojbiphy.2020.104013

[141] Shoutko, A.N. and Ekimova, L.P. (2013) Abnormal Tissue Proliferation and Life Span Variability in Chronically Irradiated Dogs. *Radiation and Environmental Biophysics*, **53**, 65-72. https://doi.org/10.1007/s00411-013-0504-7

[142] Shutko, A.N., Akushevich, I., Ekimova, L.P., Mus, V.F., Sokurenko, V.P., Yurkova, L.E. and Matiurin, K.S. (2013) The Mechanism of the Antitumor Effect of Total/Subtotal Radiotherapy with Non-Tumoricidal Doses of Radiation. *Voprosyonkologii*, **59**, 475-478.

[143] Arias, E. and Xu, J. (2022) United States Life Tables, 2020. *National Vital Statistics Reports*, **71**, 1-64.

[144] Shoutko, A.N. and Ekimova, L.P. (2017) The Effects of Tissue Regenerative Status on Hormesis in Dogs Irradiated during Their Lifespan. *Open Journal of Biophysics*, **7**, 101-115. https://doi.org/10.4236/ojbiphy.2017.73009

[145] Simsek, C., Esin, E. and Yalcin, S. (2019) Metronomic Chemotherapy: A Systematic Review of the Literature and Clinical Experience. *Journal of Oncology*, **2019**, Article ID: 5483791. https://doi.org/10.1155/2019/5483791

[146] Foster, D.S., Longaker, M.T. and Norton, J.A. (2018) The Evolving Relationship of Wound Healing and Tumor Stroma. *JCI Insight*, **3**, e99911. https://doi.org/10.1172/jci.insight.99911

[147] Assoun, S., Lemiale, V. and Azoulay, E. (2019) Molecular Targeted Therapy Related Life Threatening Toxicity in Patients with Malignancies. A Systematic Review of

Published Cases. *Intensive Care Medicine*, **45**, 988-997. https://doi.org/10.1007/s00134-019-05650-w

[148] Hager, K.K. (2016) Management of Weight Loss in People with Cancer. *Journal of the Advanced Practitioner in Oncology*, **7**, 336-338. https://doi.org/10.6004/jadpro.2016.7.3.19

[149] Dy, G.K. and Adjei, A.A. (2013) Understanding, Recognizing, and Managing Toxicities of Targeted Anticancer Therapies. *CA*: *A Cancer Journal for Clinicians*, **63**, 249-279. https://doi.org/10.3322/caac.21184

[150] NIOSH (2016) NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH), Cincinnati, Publication Number 2016-161 (Supersedes 2014-138).

[151] Blagosklonny, M.V. (2005) Carcinogenesis, Cancer Therapy and Chemoprevention. *Cells Death and Differentiation*, **12**, 592-602. https://doi.org/10.1038/sj.cdd.4401610

[152] Xiao, S., Shterev, I.D., Zhang, W., Young, L., Shieh, J.-H., Moore, M., *et al.* (2017) Sub-Lethal Total Body Irradiation Causes Long-Term Deficits in Thymus Function by Reducing Lymphoid Progenitors. *The Journal of Immunology*, **199**, 2701-2712. https://doi.org/10.4049/jimmunol.1600934

[153] Richardson, R.B., Allan, D.S. and Le, Y. (2014) Greater Organ Involution in Highly Proliferative Tissues Associated with the Early Onset and Acceleration of Ageing in Humans. *Experimental Gerontology*, **55**, 80-91. https://doi.org/10.1016/j.exger.2014.03.015

[154] Shoutko, A.N., Yurkova, L.E. and Borodulya, K. (2016) Protracted Half-Body Irradiation Instead of Chemotherapy Life Span and Lymphocytopenia in Relapsed Ovarian Cancer. *International Journal of Tumor Therapy*, **5**, 1-7.

[155] Ray-Coquard, I., Cropet, C., Van Glabbeke, M., Sebban, C., Le Cesne, A. and Judson, I. (2009) Lymphopenia as a Prognostic Factor for Overall Survival in Advanced Carcinomas, Sarcomas, and Lymphomas. *Cancer Research*, **69**, 5383-5391. https://doi.org/10.1158/0008-5472.CAN-08-3845

[156] De Kermenguy, F., Meziani, L., Mondini, M., Clémenson, C., Morel, D. and Deutsch, E. (2023) Chapter One. Radio-Induced Lymphopenia in the Era of Anti-Cancer Immunotherapy. *International Review of Cell and Molecular Biology*, **378**, 1-30. https://doi.org/10.1016/bs.ircmb.2023.03.002

[157] Garbo, R., Valent, F., Gigli, G.L. and Valente, M. (2022) Pre-Existing Lymphopenia Increases the Risk of Hospitalization and Death after SARS-CoV-2. *Infectious Disease Reports*, **14**, 20-25. https://doi.org/10.3390/idr14010003

[158] Man, Y., Stojadinovic, A., Mason, J., Avital, I., Bilchik, A. and Bruecher, B. (2013) Tumor-Infiltrating Immune Cells Promoting Tumor Invasion and Metastasis: Existing Theories. *Journal of Cancer*, **4**, 84-95. https://doi.org/10.7150/jca.5482

[159] Bushberg, J.T. (2022) Radiation Exposure and Contamination-Injuries; Poisoning. Merck Manuals Professional Edition. The National Council on Radiation Protection and Measurement Reviewed/Revised Nov.

[160] Clements, B.W. and Casani, J.A.P. (2016) Chapter 15. Nuclear and Radiological Disasters. In: *Disasters and Public Health Planning and Response*, 2nd Edition, Elsevier Inc., Amsterdam, 357-383. https://doi.org/10.1016/B978-0-12-801980-1.00015-5

[161] Miller, K.D., Nogueira, L., Mariotto, A.B., Rowland, J.H., Yabroff, K.R. and Alfano, C.M. (2019) Cancer Treatment and Survivorship Statistics. *CA*: *A Cancer Journal*

for Clinicians, **69**, 363-385. https://doi.org/10.3322/caac.21565

[162] Song, C.W., Lee, Y.-J., Griffin, R.J., Park, I., Koonce, N.A. and Hui, S. (2015) Tumor Cell Death after High-Dose Hypofractionated Irradiation: Implications for Stereotactic Body Radiation Therapy and Stereotactic Radiation Surgery. *International Journal of Radiation Oncology Biology Physics*, **93**, 166-172. http://www.sciencedirect.com/science/article/pii/S0360301615005209 https://doi.org/10.1016/j.ijrobp.2015.05.016

[163] Sheehy, E.J., Vinardell, T., Toner, M.E., Buckley, C.T. and Kelly, D.J. (2014) Altering the Architecture of Tissue Engineered Hypertrophic Cartilaginous Grafts Facilitates Vascularisation and Accelerates Mineralisation. *PLOS ONE*, **9**, e90716. https://doi.org/10.1371/journal.pone.0090716

[164] Zheng, X., Jin, W., Wang, S. and Ding, H. (2021) Progression on the Roles and Mechanisms of Tumor-Infiltrating T Lymphocytes in Patients with Hepatocellular Carcinoma. *Frontiers in Immunology*, **12**, Article ID: 729705. https://doi.org/10.3389/fimmu.2021.729705

[165] Samavat, H., Luu, H.N., Beckman, K.B., Jin, A., Wang, R., Koh, R.W., *et al.* (2020) Leukocyte Telomere Length, Cancer Incidence and All-Cause Mortality among Chinese Adults: Singapore Chinese Health Study. *International Journal of Cancer*, **148**, 352-362. https://doi.org/10.1002/ijc.33211

[166] Zhang, C., Chen, X., Li, L., Zhou, Y., Wang, C. and Hou, S. (2015) The Association between Telomere Length and Cancer Prognosis: Evidence from a Meta-Analysis. *PLOS ONE*, **10**, e0133174. https://doi.org/10.1371/journal.pone.0133174

[167] Dev, R., Wong, A., Hui, D. and Bruera, E. (2017) The Evolving Approach to Management of Cancer Cachexia. *Oncology Journal Oncology* (*Williston Park*), **31**, 23-32.

[168] Gunarsa, R.G., Simadibrata, M., Syam, A.F., Timan, I.S., Setiati, S. and Rani, A.A. (2011) Total Lymphocyte Count as a Nutritional Parameter in Hospitalized Patients. *The Indonesian Journal of Gastroenterology, Hepatology, and Digestive Endoscopy*, **12**, 89-94. https://doi.org/10.24871/122201189-94

[169] Editorial (2019) A Future Direction for Tackling Malnutrition. *The Lancet*, **395**, Article No. 2. https://doi.org/10.1016/S0140-6736(19)33099-5

[170] Zidar, D.A., Al-Kindi, S.G., Liu, Y., Krieger, N.I. and Perzynski, A.T. (2019) Association of Lymphopenia with Risk of Mortality among Adults in the US General Population. *JAMA Network Open*, **2**, e1916526. https://doi.org/10.1001/jamanetworkopen.2019.16526

[171] Deng, W., Kimura, Y., Gududuru, V., Wu, W., Balogh, A., Szabo, E., *et al.* (2015) Mitigation of the Hematopoietic and Gastrointestinal Acute Radiation Syndrome by Octadecenyl Thiophosphate, a Small Molecule Mimic of Lysophosphatidic Acid. *Radiation Research*, **183**, 465-475. https://doi.org/10.1667/RR13830.1

[172] Ajmal, L., Ajmal, S., Ajmal, M. and Nawaz, G. (2023) Organ Regeneration through Stem Cells and Tissue Engineering. *Cureus*, **15**, e34336. https://doi.org/10.7759/cureus.34336

[173] Liu, Ch., Han, D., Liang, P., Li, Y. and Cao, F. (2021) The Current Dilemma and Breakthrough of Stem Cell Therapy in Ischemic Heart Disease. *Frontiers in Cell and Developmental Biology*, **9**, Article ID: 636136. https://doi.org/10.3389/fcell.2021.636136

[174] Shoutko, A.N., Gerasimova, O.A., Fedorov, V.A. and Zherebtsov, F.K. (2019) Non-Invasive Vibration-Stress of the Cirrhotic Liver of Patients Waiting for Transplantation Induces of Circulating CD133+ Stem Lymphocytes Committed Pheno-

typically toward the Liver. *Open Journal of Biophysics*, **9**, 155-168. https://doi.org/10.4236/ojbiphy.2019.93012

[175] Ohue, Y. and Nishikawa, H. (2019) Regulatory T (Treg) Cells in Cancer: Can Treg Cells Be a New Therapeutic Target? *Cancer Science*, **110**, 2080-2089. https://doi.org/10.1111/cas.14069

[176] Sanna, P., Hadi, L.A., Jimenez, R.A.R., Hernandez, A.A.B., Zakaria, A., Sheikh, S., *et al.* (2022) Very Small Embryonic like Stem Cells: A Review of Basic Science, Applications, and Potential Use in Orthopedics. *American Journal of Biomedical Science and Research*, **17**, 88-90. https://doi.org/10.34297/AJBSR.2022.17.002377

[177] Shen, S., DeNardo, S.J., Richman, C.M., Yuan, A., Hartmann Siantar, C. and O'Donnell, R.T. (2005) Infusion after High-Dose Targeted Radionuclide Therapy Using Dosimetry. *The Journal of Nuclear Medicine*, **46**, e1034-e1041.

[178] Cattoretti, G., Orazi, A. and Gerdes, J. (1993) Proliferating Normal Bone Marrow Cells Do Stain for Ki-67 Antigen. *British Journal of Haematology*, **85**, 835-836. https://doi.org/10.1111/j.1365-2141.1993.tb03238.x

[179] Skjervold, A.H., Pettersen, H.S., Valla, M., Opdahl, S. and Bofin, A.M. (2022) Visual and Digital Assessment of Ki-67 in Breast Cancer Tissue—A Comparison of Methods. *Diagnostic Pathology*, **17**, Article No. 45. https://doi.org/10.1186/s13000-022-01225-4

[180] Jin, S., Jiang, H. and Cai, L. (2020) New Understanding of the Low-Dose Radiation-Induced Hormesis. *Radiation Medicine and Protection*, **1**, 2-6. https://doi.org/10.1016/j.radmp.2020.01.004

[181] Farooque, A., Mathur, R., Verma, A., Kaul, V., Bhatt, A.N., Adhikari, *et al.* (2011) Low-Dose Radiation Therapy of Cancer: Role of Immune Enhancement. *Expert Review of Anticancer Therapy*, **11**, 791-802. https://doi.org/10.1586/era.10.217

[182] Shoutko, A.N. and Ekimova, L.P. (2021) The Lifespan Hormesis Phenomenon in a Population Does Not Make It's Healthier. In: *Challenges in Disease and Health Research*, Vol. 5, Book Publisher International, London, 79-93. https://doi.org/10.9734/bpi/cdhr/v5/6402D

[183] Granov, A.M. and Shoutko, A.N. (2002) Paradoxes of Malignant Growth and Incompatibility of Tissues. 224 p. (In Russian)

[184] Fleming, J.M., Creevy, K.E. and Promislow, D.E.L. (2011) Mortality in North American Dogs from 1984 to 2004: An Investigation into Age-, Size-, and Breed-Related Causes of Death. *Journal of Veterinary Internal Medicine*, **25**, 187-198. https://doi.org/10.1111/j.1939-1676.2011.0695.x

[185] Lawrence, J., Ruby Chang, Y.-M., Szladovits, B., Davison, L.J. and Garden, O.A. (2013) Breed-Specific Hematological Phenotypes in the Dog: A Natural Resource for the Genetic Dissection of Hematological Parameters in a Mammalian Species. *PLOS ONE*, **8**, e81288. https://doi.org/10.1371/journal.pone.0081288

[186] Dobson, J.M. (2013) Breed-Predispositions to Cancer in Pedigree Dogs. *ISRN Veterinary Science*, **2013**, Article ID: 941275. https://doi.org/10.1155/2013/941275

[187] Shoutko, A.N., Yurkova, L.E., Borodulya, K.S. and Ekimova, L.P. (2021) New Competitive-Principal of Tumor Control by Low Dose Radiation. In: *New Frontiers in Medicine and Medical Research*, Vol. 12, Book Publisher International, London, 34. https://doi.org/10.9734/bpi/nfmmr/v12/12422D

[188] Yurkova, L.E., Shoutko, A.N., Gorkova, K.S., Ekimova, L.P., Matyurin, K.S., Bochkareva, T.N., *et al.* (2014) Indirect Control of Tumor Growth in Radiological Clinic: "Competitive" Therapy. *Academic Journal of West Siberia*, **10**, 46-48. https://s2.siteapi.org/2272b53cc9c3a55/docs/3lgbffmncbcw80gcso0kwgwk4gwwwo

[189] Kale, S., Karihaloo, A., Clark, P.R., Kashgarian, M., Krause, D.S. and Cantley, L.G. (2003) Bone Marrow Stem Cells Contribute to Repair of the Ischemically Injured Renal Tubule. *Journal of Clinical Investigation*, **112**, 42-49. https://doi.org/10.1172/JCI17856

[190] Ferrari, G., Cusella-De Angelis, G., Coletta, M., Paolucci, E., Stornaiuolo, A., Cossu G., *et al.* (1998) Muscle Regeneration by Bone Marrow-Derived Myogenic Progenitors. *Science*, **279**, 1528-1530. https://doi.org/10.1126/science.279.5356.1528

[191] Wirthlin, L., Hess, D., Zhou, P. and Nolta, J. (2008) Human Stem Cells for Tissue Repair. *Biology of Blood and Marrow Transplantation*, **14**, 151-153. https://doi.org/10.1016/j.bbmt.2007.11.011

[192] Shoutko, A.N. and Maystrenko, D.N. (2019) Spontaneous Remission of Cancer and Wounds Healing. *Austin Journal of Surgery*, **6**, 1226.

[193] Golden, E.B. and Apetoh, L. (2015) Radiotherapy and Immunogenic Cell Death. *Seminars in Radiation Oncology*, **25**, 11-17. https://doi.org/10.1016/j.semradonc.2014.07.005

[194] Janopaul-Naylor, J.R., Shen, Y., Qian, D.C., Buchwald, J.Z.S. and Bonner, A. (2021) The Abscopal Effect: A Review of Pre-Clinical and Clinical Advances. *International Journal of Molecular Sciences*, **22**, 11061. https://doi.org/10.3390/ijms222011061

[195] Shoutko, A.N., Yurkova, L.E., Borodulya, K.S. and Ekimova, L.P. (2016) Protracted Half-Body Irradiation Instead of Chemotherapy: Life Span and Lymphocytopenia in Relapsed Ovarian Cancer. *International Journal of Tumor Therapy*, **5**, 1-7.

[196] Shoutko, A.N., Yurkova, L.E., Borodulya, K.S., Ekimova, L.P. and Matyurin, K.S. (2017) Competitive Principal of Tumor Control in Radiological Clinic. *Radiology and Diagnostic Imaging*, **1**, 1-2.

[197] Shoutko, A.N., Yurkova, L.E., Borodulya, K.S. and Ekimova, L.P. (2015) Lymphocytopenia and Cytotoxic Therapy in Patients with Advanced Ovarian Cancer. *Cancer Research Journal*, **3**, 47-51. http://www.sciencepublishinggroup.com/j/crj https://doi.org/10.11648/j.crj.20150303.11

[198] Yamaura, H. and Matsuzawa, T. (1979) Tumour Re-Growth after Irradiation. *International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine*, **35**, 201-219. https://doi.org/10.1080/09553007914550241

[199] Xiong, W., Liao, Y., Qin, J.-Y., Li, W.-H. and Tang, Z.-Y. (2020) Adverse Effects of Chemoradiotherapy on Invasion and Metastasis of Tumor Cells. *Genes & Diseases*, **7**, 351-358. https://doi.org/10.1016/j.gendis.2020.04.004

[200] Schleicher, S.M., Bach, P.B., Matsoukas, K. and Korenstein, D. (2018) Medication Overuse in Oncology: Current Trends and Future Implications for Patients and Society. *The Lancet Oncology*, **19**, e200-e208. https://doi.org/10.1016/S1470-2045(18)30099-8

[201] Araki, K., Ito, Y., Fukada, I., Kobayashi, K., Miyagawa, Y., Imamura, M., *et al.* (2018) Predictive Impact of Absolute Lymphocyte Counts for Progression-Free Survival in Human Epidermal Growth Factor Receptor 2-Positive Advanced Breast Cancer Treated with Pertuzumab and Trastuzumab plus Eribulin or Nab-Paclitaxel. *BMC Cancer*, **18**, Article No. 982. https://doi.org/10.1186/s12885-018-4888-2

[202] Uriel, J. (2015) Cell Injury, Retrodifferentiation and the Cancer Treatment Paradox. *Tumor Biology*, **36**, 7365-7374. https://doi.org/10.1007/s13277-015-3981-2

[203] Liu, S., Zhang, C., Wang, B., Zhang, H., Qin, G., Li, C.C., *et al.* (2021) Regulatory T Cells Promote Glioma Cell Stemness through TGF-β-NF-κB-IL6-STAT3 Signaling. *Cancer Immunology, Immunotherapy*, **70**, 2601-2616.

https://doi.org/10.1007/s00262-021-02872-0

[204] Adini, A., Adini, I., Ghosh, K., Benny, O., Pravda, E. and Hu, R. (2013) The Stem Cell Marker Prominin-1/CD133 Interacts with Vascular Endothelial Growth Factor and Potentiates Its Action. *Angiogenesis*, **16**, 405-416. https://doi.org/10.1007/s10456-012-9323-8

[205] Kumari, N., Dwarakanath, B.S., Das, A. and Bhatt, A.N. (2016) Role of Interleukin-6 in Cancer Progression and Therapeutic Resistance. *Tumor Biology*, **37**, 11553-11572. https://doi.org/10.1007/s13277-016-5098-7

[206] Liu, H.R., Zhang, Y., Zhang, T.-X., Yuan, M., Du, C. and Zeng, P. (2021) Effects of Tocilizumab Therapy on Circulating B Cells and T Helper Cells in Patients with Neuromyelitis Optica Spectrum Disorder. *Frontiers in Immunology*, **12**, Article ID: 703931. https://doi.org/10.3389/fimmu.2021.703931

[207] Shoutko, A.N. (2019) Overview of Hematopoietic Stem Cells in Systemic Cancer Treatment, Aging, Pregnancy, and Radiation Hormesis. *Advances in Molecular Imaging*, **9**, 19-42. https://doi.org/10.4236/ami.2019.92003

[208] Muñoz, R., Girotti, A., Hileeto, D. and Arias, F.J. (2021) Metronomic Anti-Cancer Therapy: A Multimodal Therapy Governed by the Tumor Microenvironment. *Cancers* (*Basel*), **13**, Article No. 5414. https://doi.org/10.3390/cancers13215414

[209] Cazzaniga, E., Cordani, N., Capici, S., Cogliati, V., Riva, F. and Cerrito, M.G. (2021) Metronomic Chemotherapy. *Cancers* (*Basel*), **13**, Article No. 2236. https://doi.org/10.3390/cancers13092236

Abbrevations

HSC: Hematopoietic Stem Cells
PR: Proliferative Resource of hematopoietic system
NK: Normal Killer
Treg: Regulatory T cells
WBI: Whole Body Irradiation
BM: Bone Marrow
EPC: Endothelial Progenitor Cells
BMR: Base Metabolic Rate
TdT: Terminal deoxynucleotidyl Transferase
TWW: Wet Weight of Thymus
LSC: Lymphoid Stem Cells
MB: Mass of the Body
MBR: the average rate of MB increasing
sjTRECs: excision circles of extrachromosomal DNA
MPPs: Multipotent Progenitor cells
TL: Telomeres' Length
LL: Lymphoid Lineage of hematopoiesis
ML: Myeloid Lineage of hematopoiesis
ARS: Acute Radiation Syndrome
MOF: Multi-Organ Failure-dysfunction
MODS: Multi-Organ Dysfunction Syndrome
NM: Nude Mice
WBC: White Blood Cells
ECFCs: Endothelial Colony Forming cells
CIS: Chronic Inflammation Symptoms
MBR: Metabolic Base Rate
BWL: Body Weight Loss
TNM: international classification of stages of malignant neoplasms
MDS: myelodysplastic syndrome
VGEF: Vascular Endothelial Growth Factor
BWL: Body Weight Loss
RFS: Recurrence-Free Survival
NLR: Neutrophil to Lymphocyte Ratio
NCI: National Cancer Institute
WHO: World Health Organization
CR: Complete Remission
PR: Partial Remission
SD: Stable Disease
PD: Progressive Disease
NED: No Evidence of Disease
TLC: Total Lymphocytes Count
ALN: Average Number of bloods Lymphocytes

RCD: average Cancer Death' Rate
HL: Hayflick's Limit
MT: Metronomic Therapy