Scientific Research Publishing

Open Journal of Biophysics, 2025, 15(4), 55-70
https://www.scirp.org/journal/ojbiphy
ISSN Online: 2164-5396
ISSN Print: 2164-5388

Cancer Incidence Rate and Death Rate in Reverse Cardio-Oncology Are Controlled by the Variance of the Natural Level of CD34 Lymphopoietic Stemness in Different Normal Organs

Aleksey N. Shoutko[1,2*], Marat A. Karamullin[2], Michael A. Naymushin[3]

[1]Transplantology and Cell Technology Department, Granov's Russian Research Center of Radiology and Surgical Technologies, Saint Petersburg, Russia
[2]Clinical Department, Burnazyan's Federal Medical Biophysical Center of the FM & BA, Moscow, Russia
[3]Department of Radiosurgical Treatment of Complex Cardiac Arrhythmias and Electrocardiostimulation, Federal Almazov's North-West Medical Research Centre, Saint Petersburg, Russia
Email: *shoutko@inbox.ru

How to cite this paper: Shoutko, A.N., Karamullin, M.A. and Naymushin, M.A. (2025) Cancer Incidence Rate and Death Rate in Reverse Cardio-Oncology Are Controlled by the Variance of the Natural Level of CD34 Lymphopoietic Stemness in Different Normal Organs. *Open Journal of Biophysics*, **15**, 55-70.
https://doi.org/10.4236/ojbiphy.2025.154005

Received: September 16, 2025
Accepted: October 27, 2025
Published: October 30, 2025

Abstract

According to RNA markers from Human Protein Atlas, the averaged CD34 stemness together with CD31 vascularity dominates in 12- and 4-folds over the immune marker of T-cells CD2 in eighteen normal tissues. The different levels of natural CD34 stemness in tissues directly determine the incidence rate of cancer in them, as well as the cancer mortality rate, but inversely. The level of reverse cardio-oncology, *i.e.*, an increase of specific cancer hazard rate in patients with existing cardiovascular diseases (HR_{CVD}), is determined by the level of CD34 stemness of the target tissue too, but inversely. A transition from a normal to a registered malignant state of tissue is accompanied by rapid (in a few months) quantitative substitution of natural CD34 stemness with myelopoietic PODXL2 stemness, which is recognized as a predictor of multimorbidity and mortality, and the "proteomic age clock." The rapid transition of CD34 into PODXL2 stemness during malignization, which is also common for CVD and other severe illnesses, resembles a natural irreversible aging process, but is accelerated nearly tenfold. An overexpression of myelopoietic PODXL2 is secondary, originating from CD34 loss. Contributing to atherosclerosis and other cardiovascular diseases, PODXL2 is unable to reproduce lymphatic vessels and lymphocytopoiesis in the bone marrow. The primacy of CD34 loss, as the only and limited source of the lymphoid lineage of hemato-

poiesis, defines it as a real "shagreen skin" of life, as opposed to PODXL2, and in full accordance with the cause of radiation death of mammals. Accelerated aging is followed by an increase in the neutrophil-to-lymphocyte ratio (NLR) in blood, and an outstripping attrition of telomere length in lymphocytes compared with granulocytes. The rapid pathological increase in PODXL2 stemness in malignant tissues mimics a slower natural aging. It is also accompanied by a 3-6-fold acceleration of Ki67 reproductive activity in tissues for cell repair and regeneration not only in malignant tissues but in normal ones as well, which are injured lethally and sub-lethally during cytotoxic therapy. Thus, premature aging, *i.e.*, 2-5-10 years survival in oncology, is controlled by the volume of the natural resource of CD34 stemness in specific tissue, which manages the delay of metastasis. The product of the current numbers of CD34 hematopoietic stem cells and their mean Hayflick's limit is recommended as a measure of the current vital resource of the patients. This approach could reduce the wide range of speculative perspectives constantly generated by the dominant doctrine of immuno-oncology.

Keywords

Lymphocytopoiesis, Stem Cells, Morphogenesis, Tissues, Resources, Cancer, Cardiovascular Pathology, Aging, Survival, Populations

1. Introduction

The index cancer death is variable by tissue sites, being no more than 40% in patients with sites of the colorectum, bladder, kidney, endometrium, breast, prostate, and testis, but more than 40% among those with cancers of the lung, liver, pancreas, esophagus, and brain. It was also noted that the 1-year standardized mortality ratio (sMR_{CVD}) from cardiovascular diseases (CVD)after diagnosis of lung cancer is much higher (16 ± 0.99) than that after diagnosis of breast, prostate, colon, or rectum cancers (2.3 ± 0.23; $p < 0.001$). Earlier, it was explained by the toxicity of cancer treatment [1]. In turn, preexisting CVD increases the risk of lung, liver, brain, hematologic, neuroendocrine, renal, pancreas, and lymphoid cancers also, but not cancer of bladder, colon, lip, oral-head-neck, leukocytic, rectum, anus, thyroid, soft tissue, prostate, skin, ovarian, breast, or uterine [2]. These tumorigenic effects of CVD, titled "reverse cardio-oncology" phenomenon (RCO) represent a theoretical interest, especially in view of the latest uncertainties about carcinogenesis as a result of mutations [3], and the lack of any significant correlation between lifetime cancer risk and the degree of lifetime somatic clonal expansion [4].

Many risk factors and mechanisms are discussed for the bidirectional influence of cardiovascular disease and cancer on onset and progression. They include hypertension, diabetes mellitus, obesity, smoking, diet, physical activity, social determinants of health, chronic inflammation, oxidative stress, metabolic dysregu-

lation, clonal hematopoiesis of indeterminate potential, microbial dysbiosis, hormonal effects and cell senescence [5].

The multiplicity of these factors and their doubtful independence from each other [6] does not exclude the existence of a more specific, leading mechanism based on core physiology.

We already discussed the "reverse cardio-oncology" phenomenon [7] on the basis of the natural morphogenic properties of circulating hematopoietic stem CD34 cells and progenitors of lymphoid lineage, spread in different tissues unequally [8]. It was concluded that the level of residential hematopoietic "stemness" in native tissues is not identical and can act as a natural protector for the cardiovascular system and a promoter for cancer incidence in them.

In the present study, we expand comprehension of undeniable original CD34-stemness in different tissues with another member of the CD34 of the HSC family, the PODXL2 protein marker. It was not known at the time of the discovery of lethal radiation syndromes, as a result of the quantitative depletion of the germinative potency of CD133+, CD34+, and TdT+ stem lymphocytes. Today, PODXL is recognized as a member of CD34+ hematopoietic stem cells (HSCs) family and vascular-associated tissues. It spreads in tissues unequally also, and its mRNA and protein are dominant features of pluripotent stem cells, starting from oocytes up to four-cell stages, along with transient CD34 expression and further epithelial-mesenchymal transition from stable epithelial-endothelial cells into motile, invasive mesenchymal progenitor cells [9] [10]. Being one of the 20 most important age predictors, PODXL serves as a "proteomic age clock" for measuring biological age, and as a predictor of mortality and multimorbidity for fourteen age-related non-cancer diseases, together with four cancers in the population of adults [11] [12]. However, leading stem cell biologists have not yet tested PODXL in comparison with CD34 [13], as well as onco-immunologists, who have been ignoring for decades the central importance of stem cells in their field.

We found it most interesting to compare quantitatively the CD34 and PODXL2 in the range of normal tissues before and after their malignization, together with other key markers, which was considered by us earlier as proof of the dominant role of CD34 in the interplay between CVD and the risk of subsequent cancer in different organs [7].

2. Methods

To examine the relations between the content of markers of bone marrow origin in native tissues and their malignant homologues, we use the three main sources of population data.

(1) The global data (termed as consensus) of genes' expression of hematopoietic CD markers at the level of transcribed mRNA molecules (nTPM) in tissues [14]. Data for markers CD133, CD34, PODXL2, CD31, CD2, and Ki67 were extracted from and tabulated for tissues in the sequence: 1) liver (hepatocellular carcinoma), 2) pancreas (adenocarcinoma), 3) rectum (adenocarcinoma), 4) testis (germ cell

tumor), 5) brain (glioblastoma), 6) esophagus (carcinoma), 7) stomach (adenocarcinoma), 8) prostate (adenocarcinoma), 9) kidney (clear cell carcinoma), 10) colon (adenocarcinoma), 11) ovary (adenocarcinoma), 12) skin (melanoma), 13) lung (adenocarcinoma), 14) uterine (endometrial carcinoma), 15) bladder (carcinoma), 16) thyroid (carcinoma), 17) cervix (squamous carcinoma), 18) breast (invasive). The extracted data were used in the modification proposed by us earlier [8] [7]. It consists of a conversion of each tabulated nTPM value of marker i in tissue z (i_z) into the ratio i_z:i_{BM}, where i_{BM} is the same marker's value in normal bone marrow (BM), because it is the only initial source of all of them.

The ratio i_z:i_{BM} normalized to a common reference tissue, permits comparing the values of different markers with each other, ignoring the technical differences in their measurement in different tissues, which are manifested, for example, when comparing data in versions 24 and 21 of Human Protein Atlas.

Lines of tissue sites had been kept fixed throughout the present study.

(2) Five-year (2014-2019) averaged incidence and death rates of cancers standardized to US population 2000 (per 100,000) for all racial/ethnic groups, by sex [15]. Data extracted were in accordance with the range of pathology numbers 1 - 18, given in 1. Besides this, both rates were used for calculation of relative mortality in the US population.

(3) Hazard ratio (HR)for normal tissue malignization in those who have cardiovascular diseases (CVD) vs those without CVD, (HR_{CVD}). Data HR_{CVD} were extracted from [2] in accordance with the range of pathology 1 - 18, given in 1. The value of HR_{CVD} was used as a measure of the reverse cardio-oncology phenomenon.

3. Statistical Analyses

Individual parameters were evaluated statistically by calculating the mean value M, standard deviation (SD), and standard error (SE). The average values of M was compared using the t-test and the probability of p.

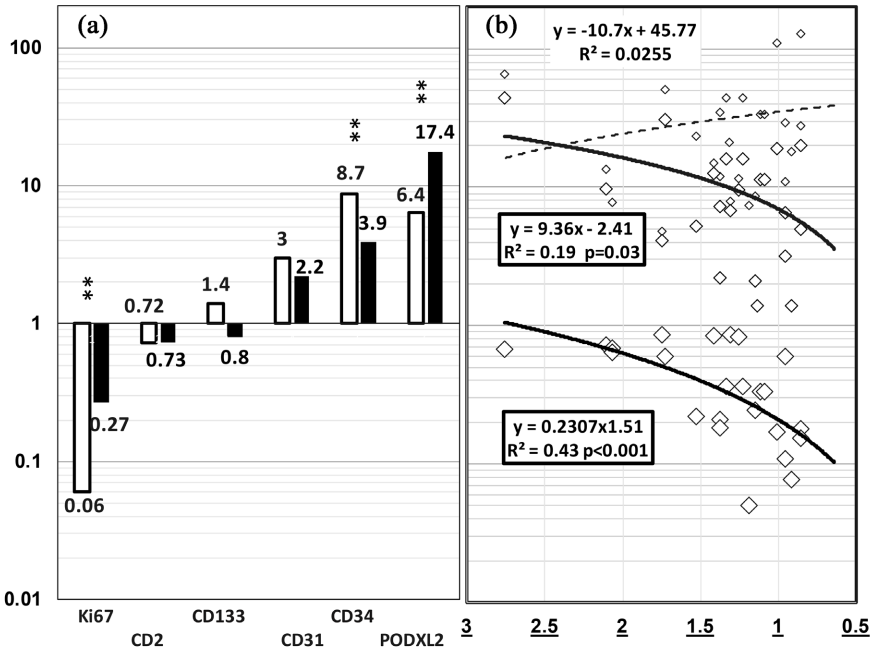
The relationship between the aggregate parameters was approximated by mathematical functions with the standard Excel program. An R^2 was used as a statistical measure of the goodness of fit of the regression line to the data. The validity of the functions' R was evaluated by the equation for the t-coefficient:

$$t = R^2 \times (n-2) \times \left(1-R^2\right) \tag{1}$$

4. Results

The values of six markers most representative for analysis in 18 tissues were extracted from [14], averaged by tissues in two groups, native and malignant, and presented in **Figure 1(a)** for comparison.

Figure 1(a) shows that the levels of two stem markers, CD34 and PODXL2, dominate in normal and malignant tissues over the CD2 marker for total immune T cells. The transition from normal to malignant status is associated with a 4-fold increase in average mitotic activity (from 0.06 to 0.27), CD34's domination before



(a) Abscissa: key protein markers in tissues. Ordinate: averaged content of markers in pairs: white columns—people without malignization; black—owners treated cancer patients during ≤ 4 months after diagnosis [14]. Asterisks: p ≤ 0.01 for white vs. black. (b) Abscissa: HR $_{CVD}$ of malignization of different tissue sites in patients with CVD (vs. non-CVD), from liver (points on the left) to breast (points on the right) [2]); the solid lines are for p ≤ 0.05, and the dotted lines are for p = not significant. Ordinate: 5-year US national cancer statistics [15]; small, middle, and big symbols are incidence rate, death rate, and cancer relative mortality rate for the 2000 US age-standardized population, which includes all racial/ethnic groups, both sexes, [15]. Solid lines and framed boxes are for valid approximation with p ≤ 0.05; dotted lines are not.

Figure 1. Distribution of averaged levels of markers in normal and malignant tissues (a), and the levels of "revers cardio-oncology" fenomenon in defferent normal tissues (b).

(8.7 vs. 3.9), and PODXL2 domination after diagnosis in ≤4 months (17.4 vs. 6.4).

Earlier, we found that the more natural (in intact tissue) the level of CD34 "stemness" (x) is, the less is the decay constant k (year^{-1}) of overall relative survival (OS = 1e^{-kt}, where t is the number of years after diagnosis) in the case of cancer:

$$k = 0.25\mathrm{e}^{-0.37x};\quad R^2 = 0.91;\ \mathrm{p} = 0.003. \qquad (2)\ [8].$$

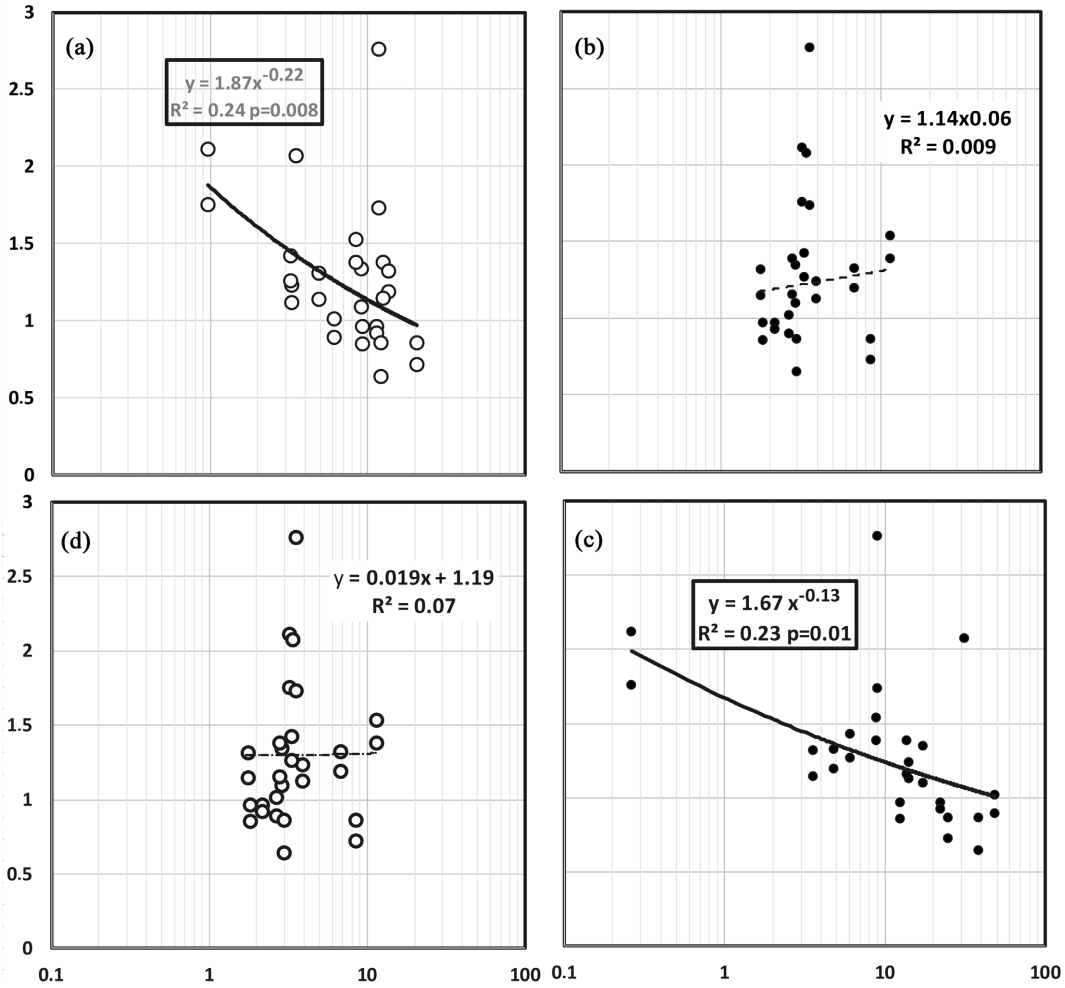
Thus, the more CD34 content there is in intact tissues (as well as its descendant CD31), the less the decay mortality constant (*i.e.*, the longer the life span), and vice versa. This result would have been expected if CD34 had delayed metastasis, *i.e.*, provided a longer development of the tumor in situ. The most reliable mechanism for this morphogenic function is improvement of vascularity and thus postponement of necrosis. This is the very function of CD34 and CD31 cells.

The "reverse cardio-oncology" phenomenon is described for patients with CVD, due to which the risk of cancer (HR $_{CVD}$) increases not evenly distributed in tissues, but gradually decreases, raising in a range from uterine, breast, prostate, skin, ovarian, rectum-anus, soft tissue, colon, leukemia, leap-oral-head-neck, bladder to pan-

creas, lymphoma, hematologic other, thyroid, renal, neuro-endocrine, lung, liver, brain ($n = 20$) [2].

According to **Figure 1(b)** HR_{CVD} values are able to predict/match the death rate from different cancers in the more extensive population of the US with a wider spectrum of morbidity reasons than CVD only [7]. In turn, CVD is the leading cause of non-cancer death in cancer survivors, and the risk of CVD mortality varies between cancers, increasing similarly to the range given above: prostate, thyroid, testicular, skin, breast, gynecologic, urological, lung, gastrointestinal, head and neck, brain [16].

Prognostic universality of HR_{CVD} is determined by its strong dependency on the level of "stemness" of intact tissues, in which cancer can arise (**Figure 2(a)**, **Figure 2(c)**). They both show that values of HR_{CVD} depend similarly on the



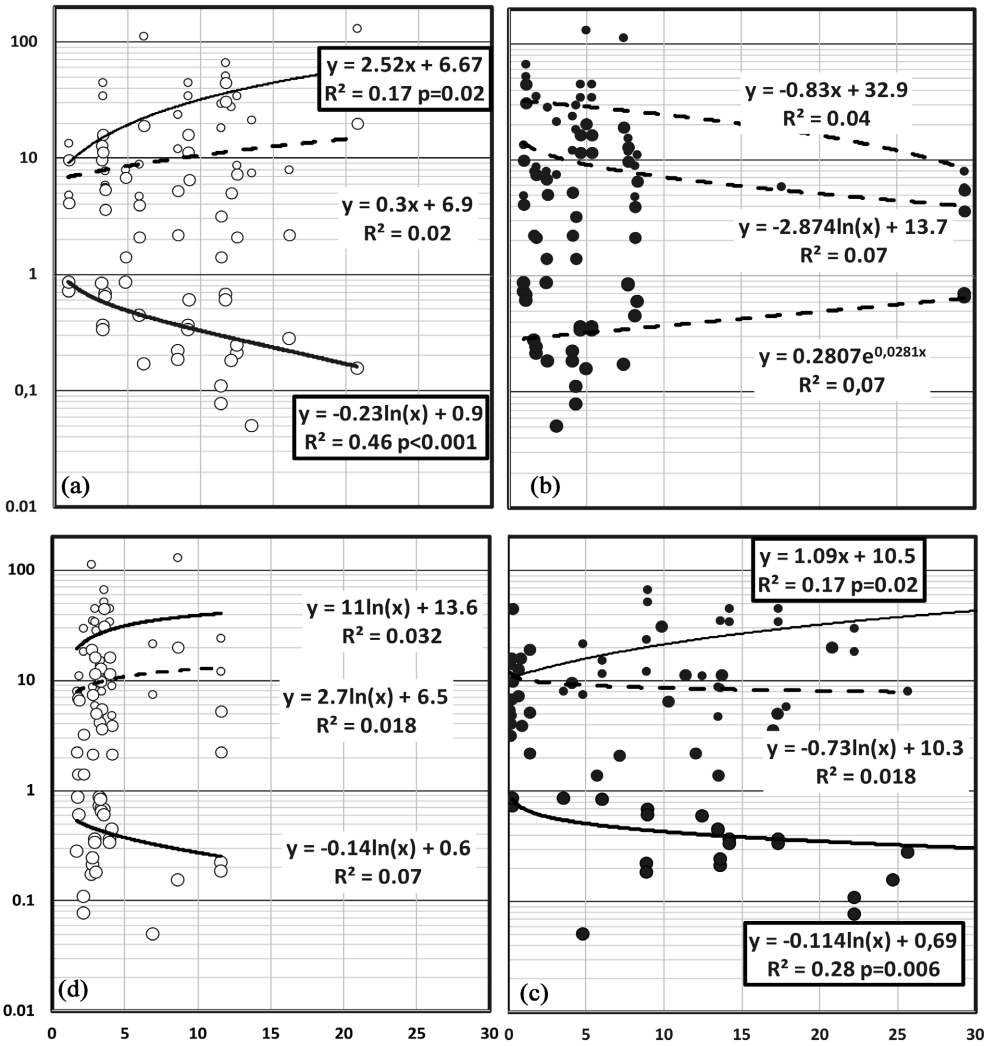
Abscissa: content of markers CD34 (upper (a) (b)) and PODXL2 (lower (c) (d)) in normal tissues (white symbols, left) and in malignant tissues (black symbols, right): from breast (maximum values on the scale) to the liver (minimum values on the scale). Ordinate: cancer HR_{CVD} for different tissue sites in patients with CVD extracted from [2].

Figure 2. A dependence of HR_{CVD} (common for atherosclerotic and non-atherosclerotic CVD) on the content of CD34 and PODXL2 in the normal tissues before and after their malignization.

contents of CD34 in intact tissues (Figure 2(a)), and on PODXL2 in malignant ones (Figure 2(c)). This almost mirror-like change since ≤ 4 months of diagnosis suggests that most of the CD34 marker transforms into, or is replaced by, PODXL2 in cancer tissue. Herewith, the greater the stemness, the lower the HR_{CVD}, *i.e.*, better vascularity of tissue. The possibility of such conversion of CD34 (x) into PODXL2 (y) within the range of tissues is confirmed by Equation (3):

$$y = -1.03x + 18.42;\quad R^2 = 0.18;\ \mathrm{p} = 0.011 \tag{3}$$

Figure 3 shows how the incidence rate, death rate, and relative mortality of



Abscissa: marker content in normal tissues (upper (a) (b)) and in malignant tissues (lower (d) (c)); CD34 (white symbols, left (a) (d)) and PODXL2 (black symbols, right (b) (c)). Tissue points are from the breast (maximum values on the scale) to the liver (minimum values on the scale). Ordinate: incidence rate, death rate, and relative cancer mortality (small, middle, and big symbols) correspond to the 2000 US standard population, including all racial/ethnic groups, both sexes [15]. p ≤ 0.05 is for solid lines and framed equations.

Figure 3. Dependence of incidence rate, death rate, and relative cancer mortality in the 2000 US standard population on the markers CD34 and PODXL2 content in different normal tissue targets before and after their malignization.

cancer in the US population depend on the content of CD34 (top) and PODXL2 (bottom) in different organs before (left) and after malignization (right), regardless of the concomitant non-cancer morbidity spectrum.

In opposition to HR_{CVD} (**Figure 1(b)**), both stem markers relate quantitatively to the parameter cancer incidence rate regardless of their origin from intact or cancer patients (**Figure 3(a)** and **Figure 3(c)**).

The normal tissues with higher natural content of CD34 reveal high cancer *incidence* rates in them (**Figure 3(a)**, $p = 0.02$). Besides this, the lowering of relative cancer mortality in this case ($p < 0.001$) is illusory/deceptive/false/artificial, being mostly a result of the increment of the denominator in the ratio "deat: incidence."

After real malignization, CD34 is simply replaced by PODXL2 (**Figure 3(c)**), which only reflects and confirms the prognostic properties of CD34, like a derivative (**Figure 2(a)**, **Figure 2(c)**).

Slight slopes of death rate curves in **Figure 3(b)** and **Figure 3(d)** are not significant, and PODXL2, being actually a stem family member, looks like a byproduct of CD34 in malignant tissues (**Figure 1(a)** and **Figure 3(a)**, **Figure 3(c)**). Thus, at the population level, we do not find proof of a direct increase in human cancer progression due to PODXL2 overexpression, as described in review [17].

Overall, **Figure 3** confirms CD34 as the leading factor of malignization in different organs, revealing a quantitative dependence of cancer incidence rate on its presence. PODXL2 rather manifests this cancer-promoting property of CD34, being an indirect witness in the same sites after malignization, but not a cause.

Thus, there is a logical chain: the existing somatic diseases, for example, CVD, can increase the death rate from cancer, in case it will join later, but only in those sites which had had a naturally lowered level of "CD34 stemness" (**Figure 2(a)**). The sites with an originally increasing level of "CD34 stemness" reveal the lack or absence of deadly influence of concomitant pathology, but have an accelerated incidence rate of cancer, which also simulates a decrease in the parameter of relative mortality.

The natural lack of CD34 and lower cancer incidence rate have lower sensitivity to concomitant non-cancer pathology but a higher mortality rate.

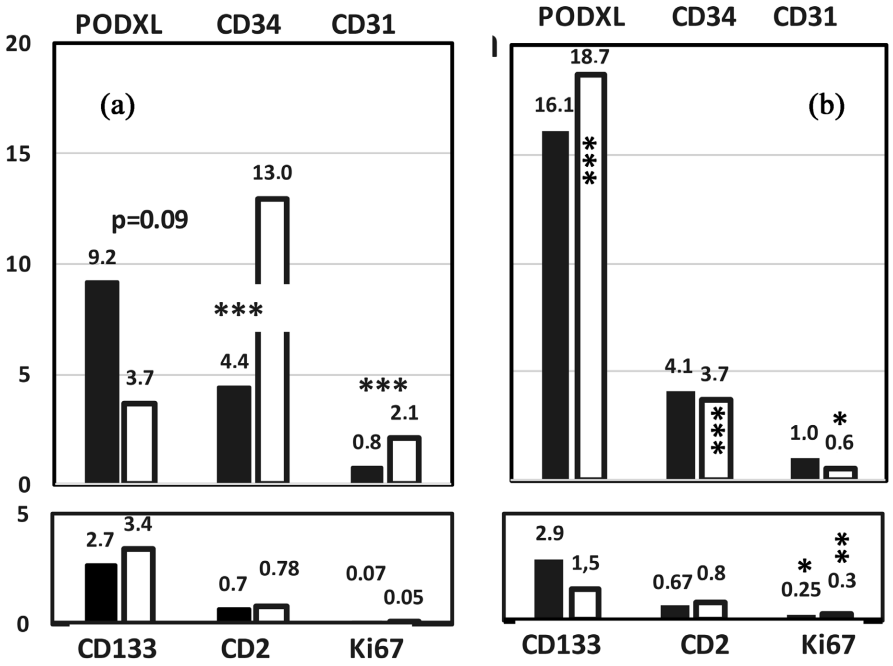
Figure 4 summarizes the main patterns and trends of markers for two parts of 18 sites: the black half, with lowered survival, such as the brain, and the white half, sites with enhanced survival, such as the breast. The columns represent the average marker content in the first half (black) and second half of the tissue sites (white).

Besides obvious confirmation of the quantitative responsibility of "CD34 stemness" for intensity of cancer incidence rate (**Figure 3(a)**, **Figure 3(b)**), **Figure 4** proves the trophic role of CD34' activity in the CD31 vasculo-angiogenesis [7].

Detailed dependence of CD31 (y) on CD34 (x) values by the range of 18 *intact* sites is a strong positive exponential curve (Equation (4)):

$$y = 0.38e^{0.11x}; \quad R^2 = 0.48; \; p = 0.02 \tag{4}$$

which becomes inverted if CD34 is replaced by PODXL2:



Abscissa: markers in tissues with reduced curability (black) and enhanced curability (white). Ordinate: content of markers in tissues, relative units. Probability p: ≤0.05, ≤0.01, ≤0.001; horizontal asterisks are for "black-white" difference, and vertical asterisks are for "a-b" difference.

Figure 4. Averaged values of markers in tissues with higher or lower curability of cancer in them. Without cancer (a), with diagnosis (b).

$$y = 1.81\mathrm{e}^{-0.09x};\quad R^2 = 0.51;\ \mathrm{p} = 0.001 \tag{5}$$

PODXL is a marker that detects arterioles and capillaries, while CD31 and CD34 detect all vessels [18].

Only high natural levels of CD31 (2.1 vs. 0.8) and CD34 (13 vs. 4.4) together predetermine successive therapy (white columns, left part of **Figure 4**). The matter of successive therapy is the strong reduction of CD31 and CD34 values to 0.6 and 3.7, respectively (white columns, right part of **Figure 4**).

The black columns for normal tissue sites are unfavorable for further. Having low natural levels of both markers (CD34 and CD31, left part of **Figure 4**), they do not respond to the treatment (black, right part of **Figure 4**). After malignization + therapy, Equation (4) has collapsed:

$$y = 0.5\mathrm{e}^{0.019x};\quad R^2 = 0.002 \tag{6}$$

and Equation (5) remains not valid/indifferent:

$$y = 0.62\mathrm{e}^{-0.009x};\quad R^2 = 0.0104 \tag{7}$$

According to Equations (4) and (6) only the favorite half of sites in the range are most sensitive to therapy because they have a high average natural level of CD34 (13.0) and CD31 markers (2.1). In other words, for successful therapy, the marker level has to be high enough to be significantly suppressed by conventional cytotoxic therapy of cancer patients (**Figure 4(b)**).

In the sites where these conditions are not fully fulfilled (black columns 4.4 and 0.8 on **Figure 4(a)**), there is no suppression of CD34 and CD31 (black columns 4.1 and 1.0 on **Figure 4(b)**), which is a matter of successful therapy.

As concerns Equation (5), PODXL2 characterizes inequality of CD31 vascularity in the range of normal tissues in opposition to CD34. PODXL2 is not sufficient to confirm the quantitative differences between the two halves of the tissue range (**Figure 4(a)**, $p = 0.09$). The prognostic secondary role of PODXL2 vs.CD34 is also accentuated by the lack of their positive dependence before malignization (Equation (5)) and after it (Equation (7)).

5. Discussion

The usefulness of bone marrow cells' transplantation had proven by the history of medicine. According to the fundamental law of mammalian radiobiology, the stem cells of lymphopoiesis (CD34+ TdT terminal deoxinucleotidyl transferase +) cells are most responsible for saving life, being supersensitive to any injuries. Success of reconstruction of hematopoiesis after ablation of bone marrow depends on the percentage of young lymphocytes in the transplant [19] [20]. The bulk number of mature lymphocytes in circulation just reflects the state of the stem-progenitor cell pool indirectly, and that is why lymphopenia is generally accepted as a biodosimeter for quantitative evaluation of viability-mortality in exposed mammals [21]. The relation of hematopoietic stem cells to morphogenesis is reconfirmed incrementally now by some of the scientific leaders in cell biology [13]. However, the vital significance of stem cells of bone marrow for the longevity of other tissues and the body as a whole is not fully recognized yet, being in the shadow of the dominant attention to immunity of matured lymphocytes, in spite of long theoretical controversy and practical inconsistency [22]-[24].

An official data of onco-immunity presents an unstable conglomerate of ad hoc's, which has been progressively increasing since the late 1800 s, when spontaneous tumor regression was first reported after bacterial infection [25] [26]. It could have been simpler and more logical if the pioneers had recognized in this phenomenon the distraction of morphogenic young lymphocytes from tumor growth [27] to the generation of real humoral immunity against microbes.

We interpreted and defined such distraction as the "competitive therapy"-forming function of stem and progenitor lymphocytes in the complex pathogenesis landscape of cancer and other diseases [28]. The history of cytotoxic therapy is marked by endless searches for a compromise equilibrium between eradication of tumor and deep lymphopenia together with other somatic harms for the body of the host [29]. To date, the hidden confusion about the anti-cancer function of matured lymphocytes extends by onco-immunologists into granulocytes, with recurring familiar ambiguities, like "are they friends or foes during cancer?", "Janus-faced role," "double-edged sword," and "the Yin and Yang profiles of neutrophils in the complex landscape of cancer pathogenesis and immunotherapy" [30]. These doubts are easily overcome by adopting the well-known slow transformation of

lymphoid to myeloid hematopoiesis with aging, which shortens lifespan naturally, and accelerated pathological consumption of the proliferative resource of lymphopoiesis for force of regenerative-repair processes at cancer, nearing an old age. PODXL stemness, prevalent in older people, is sensitive to G-M CSF and is included in the generation of myeloid cells from GEMM stem cells, in opposition to CD34.

Our data point again, that matter of conventional therapy of advanced cancer, is the reduction of the morphogenic resource of hematopoietic stem and progenitor cells. On one hand, data clearly indicate that the incidence of cancer is determined quantitatively by the natural "CD34 stemness" of an intact organ or tissue. On the other hand, HR_{CCD} in the "reverse cardio-oncology" phenomenon is absent in normal tissues with plenty of "CD34 stemness" (**Figure 1(b)** and **Figure 2(a)**). These facts point to promoter properties of CD34 stemness for cancer and a protective healing function in relation to normal tissues. On this duality, we based the idea of competitive therapy [31]. The domination of the hematopoietic stem cell CD34 marker over other ones in tissues of any origin, corresponds to the universal morphogenic function of the tissue "stemness", mostly lymphoid lineage related to the CD34 lineage of bone marrow.

Compared with CD34, the descendants of PODXL+ stem cells differentiate into granulocytes, erythrocytes, monocytes, and megakaryocytes, only expanding neutrophils [32] [33], but not lymphocytes. According to consensus data extracted from HPA (**Figure 4**), premature aging manifests with a relative decline of CD34 and an increase of PODXL2 markers via exhaustion of lymphopoiesis and its replacement by myelopoiesis in cancer patients. Notably, that shift to myelopoiesis with age explains the prevalence of cancer death rates over non-cancer diseases before 65 years old in populations of the UK and US, and vice versa after 65 [21].

The explosive loss of CD34 and shift in "stemness" toward PODXL2 in ≤ 4 months after confirmation of cancer's diagnosislooks like accelerated aging [12] [21]. Distribution of "myelopoietic" PODXL2 in cancer tissues after malignization quantitatively repeats the distribution of CD34 in them before malignization.

If the development of cancer in a certain site is attributed to the forced transition of CD34 into PODXL2 and an increase in the neutrophil-to-lymphocyte ratio (NLR) in blood, which is typical for advanced cancer, CVD, severe illness, tumors and natural aging [34] [35], it means that the cancer accumulates all signs of *thermodynamic* biological age [36]. The understanding of this is inseparably linked with the finitude or limited resource of the living system. To evaluate the resource, we have proposed to multiply the current number of lymphoid stem cells and their average telomere length [29] [37].

In comparison with granulopoiesis, the lymphopoiesis is losing of the median telomere length during normal aging 1.4 fold faster [38]. The loss of naive lymphocytes CD34+CD62+ telomeres per year is even faster (1.5-fold) than bulk lymphocytes [39]. As a result of accelerated (pathological) aging of cancer patients, a shortening of telomere length in entire blood cells during a ≤ 4-year interval since

diagnosis turns out to be 2.2-fold faster in comparison with patients free of cancer at baseline by follow-up visit [40]. That leads to shortening the lifespan of cancer patients to the practically justified and widely used parameter of 5-year survival. Besides this, risks of somatic diseases also arise, mostly as cardiovascular pathology [41].

The vascular structure is a second target for forced thermodynamic biological aging. It is well known that CD34+ and especially CD34+CD31+ cells are capable of differentiating into CD34+ endothelial cells [42]. Tumor angiogenesis begins after 3 - 5 days, with rapid increases in vascular length per volume (5-fold), but even from the 10^{th} day, the vascularity of the tumor starts irreversible involution, decreasing vascular length 2.4-fold along with an increasing neoplasm radius from 2 to 3 mm. All our values of cancer tissue markers are obtained during 4 months after diagnosis [14], *i.e.*, their values correspond to the period of involution of tumor vasculature (stained by CD34) and the existence of hypoxic areas (stained by carbonic anhydrase 9-CA9) [43]. In this view, the tissues with an original prevalence of PODXL2 over CD34 (**Figure 4(a)**, black) will progress to necrosis faster in comparison with tissues with an original prevalence of CD34. The reason for this is the high potency of PODXL stem cells to reconstitute lethally irradiated bone marrow, but mostly through enhancement of myelopoiesis [32]. The lack of functional lymphatic capillaries in solid tumors [44] can be a crucial consequence of the myeloid nature of PODXL2 dominance in them, as well as radical change of the structure of a vascular network in the tumors [43]. Besides this, PODXL2 mediates adhesion (selectins), which likely contributes to atherosclerosis, arterial and deep vein thrombosis, ischemia-reperfusion injury, and other cardiovascular diseases [45].

Unfortunately, the artificial fight against cancer remains the questionable basis of cancer therapy without accounting for the morphogenic activity of immature lymphocytes, which support cell renewal in normal and malignant tissues perceived by the host as quasi-embryonic [31].

Unavoidable post-therapeutic lymphopenia [46] and generally recognized T-cell antitumor immunity still remain axioms, although they are incompatible with idea of the lymphocytes-defenders. Conformal radiotherapy is used to reduce the volume of irradiated normal tissue, but toxic chemotherapy is used to enhance the efficacy of the radiotherapy, though it significantly increases the number and severity of "complications," including lymphopenia.

To date, the weakening of the clonal expansion HSC compartment and the stem cells of other organs is discussed as a reason contributing to the risk of cancer beyond human aging [47]. The comparison of the data [47] of clonal expansion in seven normal organs: pancreas, rectum, colon, stomach, bronchus, liver, esophagus (Equation (8)):

$$y = 4.12x + 3.48\,;\quad R^2 = 0.009\,;\ \mathrm{p} = 0.52 \tag{8}$$

with our data for CD34 in them (Equation (9)):

$$y = 0.52x + 1.18\,;\quad R^2 = 0.54\,;\ \mathrm{p} = 0.05 \tag{9}$$

shows a privilege of CD 34 stemness, as a pathogenic factor.

These few examples of occasional discrepancies are the traditional result of a rough or reckless disregard of the need to correlate one's own data more deeply with related knowledge.

6. Conclusion

In the article in question, this is a basic truth of 20th-century radiobiology, namely that lifespan is limited by the level of reproductive capacity of lymphopoiesis, as the most vulnerable system among those which control the host's life. The realization of this simple truth could completely eliminate most of the current discrepancies, but at the same time, the postulates of onco-immunology would be discredited. The expected social consequences of this collapse may frighten the scientific authorities more than the upcoming decades of theoretical and practical stagnation in the field at large [21] [48].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Zaorsky, N.G., Churilla, T.M., Egleston, B.L., Fisher, S.G., Ridge, J.A., Horwitz, E.M., *et al.* (2017) Causes of Death among Cancer Patients. *Annals of Oncology*, **28**, 400-407. https://doi.org/10.1093/annonc/mdw604

[2] Bell, C.F., Lei, X., Haas, A., Baylis, R.A., Gao, H., Luo, L., *et al.* (2023) Risk of Cancer after Diagnosis of Cardiovascular Disease. *JACC*: *Cardio Oncology*, **5**, 431-440. https://doi.org/10.1016/j.jaccao.2023.01.010

[3] Huang, S., Soto, A.M. and Sonnenschein, C. (2025) The End of the Genetic Paradigm of Cancer. *PLOS Biology*, **23**, e3003052. https://doi.org/10.1371/journal.pbio.3003052

[4] Zhang, D., Zhang, A., He, X. and Deng, S. (2024) Variation in Cancer Risk between Organs Can Not Be Explained by the Degree of Somatic Clonal Expansion. *Advanced Biotechnology*, **2**, Article No. 18. https://doi.org/10.1007/s44307-024-00025-9

[5] Wilcox, N.S., Amit, U., Reibel, J.B., Berlin, E., Howell, K. and Ky, B. (2024) Cardiovascular Disease and Cancer: Shared Risk Factors and Mechanisms. *Nature Reviews Cardiology*, **21**, 617-631. https://doi.org/10.1038/s41569-024-01017-x

[6] Kuwabara, M. (2025) The Interplay between Cancer and Cardiovascular Disease. *Hypertension Research*, **48**, 1192-1194. https://doi.org/10.1038/s41440-024-02015-9

[7] Shoutko, A.N. and Karamullin, M.A. (2024) Physiological Variance of CD34 Marker's Content in Twenty Tissues Determining Different Risks of Cardiovascular Diseases and Cancer in Them. *Open Journal of Biophysics*, **15**, 1-17. https://doi.org/10.4236/ojbiphy.2025.151001

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

[9] Kang, L., Yao, C., Khodadadi-Jamayran, A., Xu, W., Zhang, R., Banerjee, N.S., *et al.* (2016) The Universal 3D3 Antibody of Human PODXL Is Pluripotent Cytotoxic, and

Identifies a Residual Population after Extended Differentiation of Pluripotent Stem Cells. *Stem Cells and Development*, **25**, 556-568. https://doi.org/10.1089/scd.2015.0321

[10] Lin, Y., Wang, C., Phan, N.N., Chiao, C., Li, C., Sun, Z., *et al.* (2020) PODXL2 Maintains Cellular Stemness and Promotes Breast Cancer Development through the Rac1/Akt Pathway. *International Journal of Medical Sciences*, **17**, 1639-1651. https://doi.org/10.7150/ijms.46125

[11] Argentieri, M.A., Xiao, S., Bennett, D., Winchester, L., Nevado-Holgado, A.J., Ghose, U., *et al.* (2024) Proteomic Aging Clock Predicts Mortality and Risk of Common Age-Related Diseases in Diverse Populations. *Nature Medicine*, **30**, 2450-2460. https://doi.org/10.1038/s41591-024-03164-7

[12] Navas, A., Matzaraki, V., van Eekeren, L.E., Blaauw, M.J.T., Groenendijk, A.L., Vos, W.A.J.W., *et al.* (2025) Plasma Proteomic Signature as a Predictor of Age Advancement in People Living with HIV. *Aging Cell*, **24**, 1-15. https://doi.org/10.1111/acel.14468

[13] Thetchinamoorthy, K., Jarczak, J., Kieszek, P., Wierzbicka, D., Ratajczak, J., Kucia, M., *et al.* (2025) Very Small Embryonic-Like Stem Cells (VSELs) on the Way for Potential Applications in Regenerative Medicine. *Frontiers in Bioengineering and Biotechnology*, **13**, Article 1564964. https://doi.org/10.3389/fbioe.2025.1564964

[14] (2024) The Human Protein Atlas. Version 24**.** Consensus Data. https://www.proteinatlas.org/

[15] Cronin, K.A., Scott, S., Firth, A.U., Sung, H., Henley, S.J., Sherman, R.L., *et al.* (2022) Annual Report to the Nation on the Status of Cancer, Part 1: National Cancer Statistics. *Cancer*, **128**, 4251-4284. https://doi.org/10.1002/cncr.34479

[16] Ng, H.S., Meng, R., Marin, T.S., Damarell, R.A., Buckley, E., Selvanayagam, J.B., *et al.* (2024) Cardiovascular Mortality in People with Cancer Compared to the General Population: A Systematic Review and Meta-Analysis. *Cancer Medicine*, **13**, e70057. https://doi.org/10.1002/cam4.70057

[17] Le Tran, N., Wang, Y. and Nie, G. (2021) Podocalyxin in Normal Tissue and Epithelial Cancer. *Cancers*, **13**, Article 2863. https://doi.org/10.3390/cancers13122863

[18] Hong, S.P., Yang, M.J., Bae, J.H., Choi, D.R., Kim, Y., Yang, M., *et al.* (2023) Three-dimensional Morphologic and Molecular Atlases of Nasal Vasculature. *Nature Cardiovascular Research*, **2**, 449-466. https://doi.org/10.1038/s44161-023-00257-3

[19] Le Blanc, K., Barrett, A.J., Schaffer, M., Hägglund, H., Ljungman, P., Ringdén, O., *et al.* (2009) Lymphocyte Recovery Is a Major Determinant of Outcome after Matched Unrelated Myeloablative Transplantation for Myelogenous Malignancies. *Biology of Blood and Marrow Transplantation*, **15**, 1108-1115. https://doi.org/10.1016/j.bbmt.2009.05.015

[20] Müller, A.M.S., Poyser, J., Küpper, N.J., Burnett, C., Ko, R.M., Kohrt, H.E.K., *et al.* (2014) Donor Hematopoiesis in Mice Following Total Lymphoid Irradiation Requires Host T-Regulatory Cells for Durable Engraftment. *Blood*, **123**, 2882-2892. https://doi.org/10.1182/blood-2013-10-530212

[21] Shoutko, A.N. (2024) Time for a New Paradigm in Oncology? Viewpoint of the Radiobiologist. *Open Journal of Biophysics*, **14**, 11-55. https://doi.org/10.4236/ojbiphy.2024.141002

[22] Shoutko, A.N. (2021) Self or Not-Self Is Malignant Tissues for the Host? In: *New Frontiers in Medicine and Medical Research Vol.* 10, Book Publisher International (a part of Science Domain International), 110-123. https://doi.org/10.9734/bpi/nfmmr/v10/12421d

[23] 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

[24] Shoutko, A.N., Mus, V.F. and Maystrenko**,** D.N. (2020) Peripheral Signs of Lymphocytopoiesis in the Prediction of the Terminal Life Span of Cancer Patients. In: *Current Topics in Medicine and Medical Research*, Hugh Howey, 139-153. https://www.researchgate.net/publication/344470778

[25] Shoutko, A.N. (2019) Immunity or Morphogenesis in Cancer Development and Treatment. *Integrative Cancer Science and Therapeutics*, **6**, 1-8.

[26] 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

[27] Shoutko, A.N. and Maystrenko, D.N. (2019**)** Spontaneous Remission of Cancer and Wound Healing. *Austin Journal of Surgery*, **6**, 1-4.

[28] Shoutko, A.N., Yurkova, L.E, Borodulya, K.S., Ekimova, L.P., Matyurin, K.S. (2017**)** Competitive principle of tumor control in a radiological clinic. *Radiol Diagn Imaging*, OAT, **1**(2), 1-2. ISSN: 2515-0200, doi: 10.15761/RDI.1000107

[29] Shoutko, A.N. and Ekimova, L.P. **(**2021) The Lifespan Hormesis Phenomenon in a Population Does Not Make Its Healthier. In: Veeramuthumari, P., Ed., *Challenges in Disease and Health Research*, BP International, 79-93.

[30] Huang, X., Nepovimova, E., Adam, V., Sivak, L., Heger, Z., Valko, M., *et al.* (2024) Neutrophils in Cancer Immunotherapy: Friends or Foes? *Molecular Cancer*, **23**, Article No. 107. https://doi.org/10.1186/s12943-024-02004-z

[31] 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.

[32] Doyonnas, R., Nielsen, J.S., Chelliah, S., Drew, E., Hara, T., Miyajima, A., *et al.* (2005) Podocalyxin Is a CD34-Related Marker of Murine Hematopoietic Stem Cells and Embryonic Erythroid Cells. *Blood*, **105**, 4170-4178. https://doi.org/10.1182/blood-2004-10-4077

[33] Li, P., Karaczyn, A.A., McGlauflin, R., Favreau-Lessard, A.J., Jachimowicz, E., Vary, C.P., *et al.* (2017) Novel Roles for Podocalyxin in Regulating Stress Myelopoiesis, Rap1a, and Neutrophil Migration. *Experimental Hematology*, **50**, 77-83. https://doi.org/10.1016/j.exphem.2017.04.001

[34] Paganelli, R. and Di Iorio, A. (2025) The Neutrophil-to-Lymphocyte Ratio in Aging and Immunosenescence. *Exploration of Immunology*, **5**, Article 1003200. https://doi.org/10.37349/ei.2025.1003200

[35] Wang, S., El Jurdi, N., Thyagarajan, B., Prizment, A. and Blaes, A.H. (2024) Accelerated Aging in Cancer Survivors: Cellular Senescence, Frailty, and Possible Opportunities for Interventions. *International Journal of Molecular Sciences*, **25**, Article 3319. https://doi.org/10.3390/ijms25063319

[36] Tarkhov, A.E., Denisov, K.A. and Fedichev, P.O. (2024) Aging Clocks, Entropy, and the Challenge of Age Reversal. *Aging Biology*, **2**, Article 20240031. https://doi.org/10.59368/agingbio.20240031

[37] 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

[38] Vaiserman, A. and Krasnienkov, D. (2021) Telomere Length as a Marker of Biological

Age: State-of-the-Art, Open Issues, and Future Perspectives. *Frontiers in Genetics*, **11**, Article 630186. https://doi.org/10.3389/fgene.2020.630186

[39] Lansdorp, P.M. (2022) Telomeres, Aging, and Cancer: The Big Picture. *Blood*, **139**, 813-821. https://doi.org/10.1182/blood.2021014299

[40] Hou, L., Joyce, B.T., Gao, T., Liu, L., Zheng, Y., Penedo, F.J., *et al.* (2015) Blood Telomere Length Attrition and Cancer Development in the Normative Aging Study Cohort. *EBioMedicine*, **2**, 591-596. https://doi.org/10.1016/j.ebiom.2015.04.008

[41] Xu, C., Wang, Z., Su, X., Da, M., Yang, Z., Duan, W., *et al.* (2020) Association between Leucocyte Telomere Length and Cardiovascular Disease in a Large General Population in the United States. *Scientific Reports*, **10**, Article No. 80. https://doi.org/10.1038/s41598-019-57050-1

[42] Forghani, A., Koduru, S.V., Chen, C., Leberfinger, A.N., Ravnic, D.J. and Hayes, D.J. (2019) Differentiation of Adipose Tissue–Derived CD34+/CD31− Cells into Endothelial Cells *in Vitro*. *Regenerative Engineering and Translational Medicine*, **6**, 101-110. https://doi.org/10.1007/s40883-019-00093-7

[43] Forster, J.C., Harriss-Phillips, W.M., Douglass, M.J.J. and Bezak E. (2017) A Review of the Development of Tumor Vasculature and Its Effects on the Tumor Microenvironment. *Hypoxia*, **5**, 21-32. https://doi.org/10.2147/hp.s133231

[44] Leu, A.J., Berk, D.A., Lymboussaki, A., Alitalo, K. and Jain R.K. (2000) Absence of Functional Lymphatics within a Murine Sarcoma: A Molecular and Functional Evaluation. *Cancer Research*, **60**, 4324–4327.

[45] McEver, R.P. (2015) Selectins: Initiators of Leucocyte Adhesion and Signalling at the Vascular Wall. *Cardiovascular Research*, **107**, 331-339. https://doi.org/10.1093/cvr/cvv154

[46] U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute (2006) Common Terminology Criteria for Adverse Events (CTCAE)/Version 3.0 Amgen Oncology. https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v3.pdf

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

[48] Duhamel, M. and Salzet, M. (2025) Self or Non-Self: End of a Dogma? *Frontiers in Immunology*, **16**, Article 1595764. https://doi.org/10.3389/fimmu.2025.1595764