VIEWPOINT

Immune by heart: accidental observations inspiring perspective therapeutic/preventive strategies against cancer

Filippo Minutolo*[a]

Dedicated to all nonscientists driven by curiosity.

[a] Prof. F. Minutolo, ORCID 0000-0002-3312-104X
Dipartimento di Farmacia
Università di Pisa
Via Bonanno 33, 56126 Pisa, Italy
E-mail: filippo.minutolo@unipi.it

Abstract: We often overlook banal events that take place under our eyes. Instead, they might represent inspiring sources for revolutionary scientific discoveries. Simple observations, such as those regarding the substantial immunity of the heart to cancer or the non-invasive behavior of plant tumors, are just iceberg tips hiding profound mechanistic causes that deserve deeper investigations. Several existing or unprecedented approaches aimed at improving both prevention and treatment of tumors are herein indicated on these bases. This viewpoint does not intend to give definitive answers, but rather to provide cues for discussion and motivations to engage unexplored and accessible strategies to fight cancer.

Personalized *vs.* generalized medicine

One of the most crucial questions for medicinal chemists while struggling to create innovative drugs is: "Are we hitting the right target?" This is especially puzzling when it comes to anticancer agents, due to the high heterogeneity displayed by different tumor types, organs involved, stage of the disease, mutations, etc. etc.
A very large number of novel cancer targets have been so far identified. Many of these targets derive by an extremely complex analysis of mutations found in neoplastic cells. However, only a minor portion of them can be considered as driver gene mutations, which are those conferring a selective growth advantage, and they are difficult to spot among the numerous somatic mutations. Furthermore, the recurrence rates of driver mutations usually are quite low even within the same tumor type.[1]
Most medicinal chemists (*myself for sure!*) have difficulties in understanding and handling the huge amount of information concerning all the significant recurring mutations for the development of new anticancer agents. Therefore, I would suggest a provocative approach, which is opposite to that deriving from "personalized" medicine and pharmacogenomics strategies. In fact, as medicinal chemists we can be confident that essential insight on these tactics may derive from current and future studies carried out by researchers working in other fields such as Medical and Biological Sciences. Anyway, will personalized medicine be affordable and accessible by the majority of cancer patients in the near future? Meanwhile, would not it be convenient to work also on some common-sense aspects and seek for more "generalized" tactics against malignant neoplastic diseases?

Many scientific discoveries have so far derived from unexpected observations, although these were obviously followed by accurate scientific investigations. A classic example: bacteria do not grow in rotten culture media; this led to the discovery of antibiotics. It should be acknowledged that, since the discovery of penicillin, there have been continuous monitoring activities of bacterial mutations in order to produce new drugs that overcome antibiotic resistance. Nevertheless, the starting point of the β-lactam antibiotic era was a banal event.
In anticancer therapy, unfortunately, a first accidental step similar to that of penicillin is still missing. As a matter of fact, we still have not found a class of drugs that efficiently kills all cancer cells with no or minimal toxicity to normal cells. We are already working on mutation analysis, occurrence of drug resistance, and personalized medicine, which are often efficient, but our anticancer therapeutic "column" has not been built on a solid "plinth", as of yet.
This viewpoint article is intended to indicate only some of the observations often reported also by nonscientists, in an attempt to build a reasonable picture that may inspire the scientific community to discover revolutionary antitumor agents or, else, to identify preventive measures and behaviors that can impact health policies.

Heart is substantially immune to cancer

Cancers are usually found in every bodily organ or system, although with various degrees of incidence rates. On the contrary, tumors of the heart are highly unusual and they generally start somewhere else in the body before spreading to the heart. Most (about 75%) of the very small portion of tumors that start in the heart are benign, whereas malignant primary heart tumors, known as cardiac sarcomas, are extremely rare.[2]
Why are heart cancers so particularly exceptional as If they did not occur at all? And yet, heart is largely perfused and exposed to all carcinogens present in the blood flow, at least as much as most of the other organs in our body.

Impaired cell division… ?

Some could argue that *cell division* in cardiomyocytes is very limited (turnover of less than half of them during a normal life span).[3] Therefore, their inborn block of cell proliferation constitutes a protection against cancer. Nevertheless, neurons do

not undergo cell division either. Still, unfortunately, deadly cancers originating in the CNS are quite diffused among humans. Hence, this is not likely to be the real reason.

…or tireless metabolic activity?

Instead, this phenomenon may be related to *metabolism*. It is well-known that the heart never rests (it'd better not!). It is constantly working and burning nutrients by oxidative metabolism, with no accumulation or deposit of energy reservoirs in the form of fat, which also results in a lower accumulation of lipophilic toxins. Conventional wisdom says that "*it is usually preferable to drink continuously flowing spring water than standing water of a stagnant pond*". A continuous and efficient oxygen-consuming metabolism seems to be the key to this phenomenon. In fact, cardiomyocytes have a major limitation: they cannot contract in the absence of oxygen. Therefore, their indefatigable activity always occurs by means of aerobic mechanisms, as demonstrated by the high mitochondrial density present in these cells. Cardiomyocytes utilize also lactic acid to produce energy by means of its oxidation back to pyruvate. This is in sharp contrast with what happens in tumors, where cancer cells often adopt the glycolytic phenotype (*Warburg effect*) as a selective growth advantage feature, which is characterized by a predominant conversion of glucose to lactic acid. Actually, the metabolic profile of cancer cells within tumors is quite complex and represented by a highly heterogeneous situation where there are various metabolic sections collaborating with each other in order to guarantee cancer progression.[4] The metabolic plasticity of tumor cells reflects their ability to survive also in hostile environments, such as tumor hypoxia, and to adapt to the continuous environmental changes occurring during cancer progression. Nevertheless, it is clear that, while *tumor tissues globally produce an excess of lactic acid* in the surrounding tissues, which promotes tissue invasion, metastasis, angiogenesis and immune escape, *the heart recycles lactate* deriving from other compartments and utilize it as a fuel.

Furthermore, the efficiency of the energy-producing oxidative process in the heart is much higher than that followed by most cancer cells. In fact, *tumors need large amounts of glucose* to survive and, therefore, their progression benefits from abundance of nutrients. It is not a case that there is a clear link between obesity and several types of cancer in humans, although the role of the adipose tissue in cancer progression is not limited to the supplying of extra-nutrients, but it also involves production of adipokines (TNF-α, IL-6, etc.), as well as promotion of inflammation and insulin resistance.[5] Right, insulin and insulin-like growth factors (IGF1 and IGF2) are known to promote cancer development and progression, as well as drug resistance[6] and insulin resistance generally leads to increased levels of circulating insulin (hyperinsulinemia). This raises a personal speculative consideration: as opposed to heart cells, pancreatic cells are "soaked" in insulin; is this why pancreatic cancers (regardless their exocrine/endocrine origin) are so aggressive?

Plants tumors do not metastasize

Cancer, intended as an unrestrained proliferation of abnormal cells, affects both animals and plants. However, tumors cannot metastasize in plants, therefore the formation of metastases has to be related with circulation.

Actually, the circulatory system is the means of transport of nutrients, waste products and CO_2/O_2 in both plants and animals. The main difference is that, differently from plants, animals do have cells circulating through the blood flow and the lymphatic system. Should this be the really significant difference? Maybe plant tumors do not metastasize because plant cells do not move around, contrary to what happens to some animal cells.

If this is the real issue, I believe we should look more carefully at a possible role played by our circulating cells in the process of tumor dissemination. Of course, our immune system plays a fundamental role to counteract many pathologies, including infections and cancer. In fact, activation of T cell responses often results in the control of cancer progression, because these lymphocytes can spot tumor antigens and activate their effector programs even within neoplastic tissues. This aspect constitutes the basis for success of *anticancer immunotherapy* against a considerable number of cancer types.

On the other hand, there is growing evidence that some specific classes of white blood cells, such as *macrophages* and *neutrophils*, are involved in a kind of "betrayal", which make them "accomplices" in cancer malignancy.

Macrophages

Macrophages constitute a first line of defense of our immune system and are devoted to phagocyte cells that are considered to be a threat to our body. However, in cancer the normal function of macrophages is often found to be disrupted, so that tumor-associated macrophages (TAMs) can be either tumor killing (M1) or tumor promoting (M2). Thus, the M2-type of TAM starts to promote tumor growth and invasion. This is thought to be due (at least in part) to the chronic inflammation present in the tumor microenvironment (TME) and to the consequent release of inflammatory factors. TAMs were found to directly interact with cancer cells and to protect them from radio- and chemotherapies by means of their innate tissue repair response. Furthermore, they are able to promote angiogenesis and immunosuppression when within the TME.[7]

Neutrophils

Neutrophils constitute the most abundant immune cells in humans, representing 50–70% of all leukocytes. These cells have been considered for quite a long time as an unimportant component of TME, although more recently there is evidence that they do not really assume a "neutral" behavior in cancer.[8] Actually, there is an ongoing discussion about how and when these cells display pro-tumor or anti-tumor properties, since they have been reported to either oppose or potentiate the development of neoplastic diseases. More recent investigations seem to attribute an important role to tumor-associated neutrophils (TANs) in tumor progression.[7] In fact, tumors exploit several pathways to disrupt normal neutrophil activities and to make them accomplices in the progression of the disease.

The mechanism by which neutrophils promote tumor initiation, growth and metastasis is not completely clear. However, it is known that neutropenia induced by chemotherapy is often associated with improved survival in patients with various types of cancer.[9]

There is clinical evidence supporting the count of neutrophils and, in particular, the neutrophil to lymphocyte ratios (NLRs), as biomarkers for the prediction of cancer recurrence or progression. In fact, a reduction of these parameters during therapy or after

surgery is generally an indication of a good response, whereas a rise in their value is associated to a poor prognosis.[10]

It is now well-established that inflammation plays a key role in cancer and neutrophils can be considered as a crucial link between the inflammatory process and malignant neoplasms. However, the way by which neutrophils promote tumor development is not entirely understood. For sure, not all neutrophils are equal, but they are subject to phenotypic changes that are sensitive to the control operated by tumor-derived factors, which enhance the immunosuppressive properties of neutrophils. Neutrophils are also known to be promoters of angiogenesis, which contributes to tumor growth and cancer cell extravasation into the bloodstream. Furthermore, neutrophil extracellular traps (NETs), which are generally employed to capture and eradicate invading microbes, are also used to recruit circulating cancer cells and guide them into distant organs, thus promoting the formation of metastases.[11] Actually, neutrophils were found to concentrate in distant organs earlier than cancer cells start colonizing those compartments, thus generating the so-called "premetastatic niche". This preliminary accumulation was found to be promoted by tumor-derived factors.[12] Currently, there is an important need to develop reliable models in order to finally establish the timing and mechanisms by which neutrophils support cancer progression, so that we may find suitable targets to be exploited for therapeutic interventions. Since these immune cells do not live long in *ex vivo* cultures, their behavior should be necessarily studied *in vivo*.

Dwarfism, age, diabetes and cancer risk

A community of people in Ecuador displaying a *Laron-type dwarfism* was observed for more than 20 years and they turned out to be substantially *immune to cancer and diabetes*. These individuals carry mutations in the growth hormone receptor (GHR), which leads to an *insensitivity to growth hormone* (GH), with consequent short stature. This syndrome also causes a *deficiency of IGF1* and a concomitant increased sensitivity to insulin (thus no diabetes!).[13] On the contrary, it was demonstrated, that *height is associated with increased risk of cancer and cancer death*. This phenomenon does not seem to be related to the higher number of cells present in taller people. It rather depends on genetic and hormonal factors, in particular, on the GH/IGF1 axis, which is stimulated also by nutrition during childhood and adolescence.[14] Should we then correlate the *age-dependent life-long decrease of GH and IGF1 levels* with the fact that *certain types of cancer are more aggressive in younger than older patients*?

On the other hand, subjects with type-2 diabetes (reduced insulin sensitivity) present a remarkable increase in the pancreatic cancer risk.[15] Furthermore, metformin, an anti-diabetic drug, displayed a significant anticancer activity in diabetics,[16] although it is still not clear if its efficacy against tumors depends on its action on the electron transport chain (ETC) of cancer cells or rather on the *reduction of systemic insulin and glucose levels* caused by this drug.

Possible therapeutic/preventive strategies

Patients should always be warned against fraudulent or ignorant medical practices promoted by charlatans with no scientific evidence supporting their efficacy and safety. Nevertheless, currently available therapies, which are often curative, in some cases would benefit from the assistance of other types of interventions. I would skip the discussion of most obvious preventive recommendations, such as "do not smoke", "drink less alcohol" and "protect your skin from sun exposure". However, there are other suggestions for cancer prevention/therapy that are related to some of the observations described in the previous sections.

"Follow your heart": physical activity, proper diet/caloric restriction mimetics, lactate-lowering anti-glycolytic agents.

Obesity (remember: heart has no fat deposits) was found to be associated to an increased risk of cancer affecting different sites, such as colon, esophagus, stomach, kidney, breast, uterus, liver, gallbladder, pancreas, prostate, ovary, thyroid, meninges (meningioma) and plasma cells (multiple myeloma).[17] Therefore, anti-obesity interventions would be valuable preventive strategies, although they need to be controlled and well-balanced, otherwise an extreme weight loss may cause cachexia or neutropenia. Some of the measures aimed at reducing excess weight are discussed below.

Non-strenuous *physical activity* was found to be related to lower risks of several types of cancer, with the single exception of malignant melanoma (probably due to the higher non-protected exposure to sunlight related to outdoor leisure activities). Therefore, sedentary adults should be educated by health care professionals about this fundamental instrument of prevention and cure.[18]

Over the past few millennia, health benefits deriving from *periodic fasts* dictated by the most diffused religions on earth might have constituted an evolutionary advantage, since they are now being recognized as therapeutic and preventative interventions against several afflictions. They should be reconsidered even on the basis of scientifically rational concepts and properly modulated in accordance with specific needs. So *low-calorie diets*, *caloric restriction mimics* and/or *periodic fasting* are effective ways to prevent cancer or to improve the efficacy of anticancer therapies.[19] For example, short-term starvation proved to sensitize various cancer cell types to chemotherapy in both *in vitro* and *in vivo* models. This intervention promoted apoptosis and an anti-Warburg effect, consisting in an increased oxygen consumption and a reduced glycolysis (remember: heart is constantly active by means of an oxidative metabolism).[20] There is some evidence suggesting that consumption of some food stimulating the GH/IGF1 axis should be limited. As mentioned above, GH, IGF1, and insulin are now being considered as key mediators of tumor development, and scientists are trying to figure out how to use this information to develop therapeutic strategies. For example, insulin-lowering agents, such as metformin[16] or diazoxide[21] have already shown some promising preclinical results against neoplastic diseases. Meanwhile, some foods were also identified as strong promoters of the GH/IGF1 pathway, such as milk and dairy products, whose consumption was positively associated with an increased risk of cancer by means of an increase of the levels of IGF1.[22] The impact of a high protein intake, especially milk proteins, on the stimulation of growth is made evident by the dramatic increase in the average height of some populations in Europe over the past century. For example,

the tallest people over these years are the Dutch, whose average heights is 182 cm, starting from a value of only 168 cm one century before.[23] The Dutch are amongst the main consumers of milk and dairy products in the world *(I have to admit milk is so good in the Netherlands!)*. Dairy product intake especially during childhood and puberty might be the cause of such a stunning change because of the potent stimulation of the GH/IGF1 pathway. This type of feeding would not be so essential in adults. It is still not clear if this population present higher risks of developing tumors (taller people do show greater risk, though[14]), but all these data would indicate that a *reduction in the intake of milk and dairy products during maturity* may be beneficial. A few years ago a 4-fold increase in cancer death risk was found to be associated to individuals aged 50–65 reporting high protein intake, thus suggesting dietary intervention with a reduced protein intake to prevent cancer.[24] Furthermore, pharmacological attempts to disrupt the IGF1 action were carried out with *somatostatin analogues*, since these drugs had already been approved for the treatment of acromegaly. Similarly, an antagonist of the GH receptor, *pegvisomant* (another drug used for treating acromegaly) is currently being considered as a perspective anticancer agent, since it is able to significantly reduce the plasma levels of IGF1.[25]

Going back to *lactate*: the heart efficiently burns it in an oxidative way to produce energy and CO_2. On the contrary, tumors produce massive amounts of lactic acid, which promotes immune-escape, resistance, angiogenesis, tumor invasion and metastasis formation.[26] Therefore, lactate should now be considered both as a *diagnostic biomarker* and as a *therapeutic target*.

Early diagnosis of tumors still constitutes one of the major challenges in oncology. Unfortunately, the most reliable techniques, such as PET/CT scan and magnetic resonance imaging (MRI), cannot be utilized for high-throughput screening of a large population. Even the low-dose computed tomography (LDCT) is expensive and presents a high rate of false-positive, together with the exposure to potentially harmful radiation doses. More recently, the use of *our best friends (or doctors?), the dogs,* for the early diagnosis of cancer is emerging as a very promising preventive strategy. This approach is supported by the fact that dogs have a very sensitive olfaction, so they detect the altered production of metabolites in human cancer. So far, scientists have focused their attention to a specific class of metabolites, called Volatile Organic Compounds (VOCs), such as some types of aliphatic aldehydes, whose production is enhanced in cancer. This has led to development of analytical techniques and sensors ("electronic noses") that are able to detect these substances even in the absence of a canine companion.[27] However, the profile of VOCs varies considerably in different tumor types, whereas dogs do not seem to be influenced by the type of cancer they were trained for. It was later hypothesized that cancer cells have a unique odor pattern, regardless the different types of cancer.[28] *Could this common smell derive from lactic acid?* This compound is not as volatile as VOCs (it does smell, though!), but it already proved to be a potent mosquito attractant. *Detection of lactate* has been so far limited only to a few medical practices, mainly involving the monitor of sport activities in athletes. Therefore, we now have the technology (it can be easily improved for *ad hoc* applications) to screen large portions of population for abnormal production of lactate. Although the utility of this potential biomarker still needs to be fully demonstrated, it may be used for a first-line high-throughput screening of cancer, before submitting patients to more specific CT or MRI scans for a confirmation of the diagnosis. Detection of lactate can be carried out in a series of specimens, depending on the sensitivity required and on the location of the tumor. While a quantification of this metabolite in the blood may be poorly sensitive and subject to a large number of interferences (in this case, serum levels of lactate-producing enzyme LDH-A are considered as a more reliable prognostic marker[29]), an analysis of lactic acid in exhaled breath may be used for an advance warning of lung cancer. Similarly, stool (colorectal), urine (bladder, kidney), saliva (oral), etc. may be utilized for early detection of other types of cancer. Of course, the use of *lactic acid as a biomarker* will result in many false positive cases, because overproduction of lactate may be due to several other concomitant conditions, such as strenuous physical exercise, fatigue, infections etc. Nevertheless, I believe it is worth a shot and trials for its validation should be implemented as soon as possible.

A particular attention should be dedicated to the clinical use of *lactate in parenteral formulations*, due to its above-mentioned activities supporting cancer progression. There are solutions such as, for example, Ringer's lactate or Hartmann's solution, which are often utilized after surgery or losses of body fluid. It would probably be advisable to replace them with analogous lactate-free solutions, especially in cancer patients, since there might be a non-negligible risk of boosting diffusion of cancer cells in the whole body and formation of metastases.

From a therapeutic point of view, any intervention aimed at *interfering with the peculiar metabolism of tumors characterized by the overproduction of lactic acid* should be considered as a promising approach for the development of new *anti-glycolytic agents* against cancer. This is a rapidly emerging field where medicinal chemists should definitely concentrate their efforts, because the clinical development of anti-glycolytic drugs is not adequate, as of yet. In fact, only a very limited number of candidate drugs that modulate cancer glycolysis have entered clinical trials. Some of the most representative examples are: AG-348, a pyruvate kinase (PK) activator; AZD3965, a monocarboxylate transporter 1 (MCT1) inhibitor; dichloroacetate (DCA), a pyruvate dehydrogenase kinase (PDK) inhibitor; AT-101 (gossypol-acetate complex) an inhibitor of lactate dehydrogenase (LDH) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH); 2-deoxyglucose (2-DG) and 3-bromopyruvate (3BP), inhibitors of various key glycolysis enzymes; lonidamine, a hexokinase (HK) and MCT1 inhibitor; silybin, a natural product that blocks glucose transporters (GLUTs),[30] To the best of my knowledge, none of them has yet received final approval for clinical use. Therefore, a more intensive effort in this strategy is urgently needed.

"Real eyes realize real lies": so neutralize non-neutral neutrophils!

Wise men say: "Beware of your friends more than your sworn foes!". Our immune cells (remember: plants do not have them) are generally "friends", which occasionally might even turn into enemies. Therefore, any successful therapeutic intervention should: *a)* fortify the "good cops"; *b)* spot the "betrayers" and destroy them.

Anticancer immunotherapies that increase the capacity of endogenous T cells to eliminate malignant cells have proved therapeutic efficacy in a wide panel of human cancers. In particular, there are tumor-specific antigens, called neoantigens,

whose recognition is now considered as a foremost cause in the positive outcome of immunotherapies in the clinic. So, in the future it will be essential to develop immunotherapies that selectively enhance neoantigen-specific T cell reactivity, in order to obtain high specificity and safety.[31] In parallel, there are other "trivial" options that might be more easily applied. For example, a certain degree of stimulation of anticancer T cell responses can also be obtained by some chemotherapeutic agents (for example, doxorubicin). In this frame, caloric restriction was recently demonstrated to improve this anticancer immune response. In fact, the effect of a *fasting-mimicking diet* or *caloric restriction mimetics* (such as hydroxycitrate) increased the number of "good" tumor infiltrating $CD8^+$ cytotoxic T cells, leading to an improvement of the therapeutic outcome.[32]

On the other hand, as mentioned above, some immune cells are now being considered as partners in tumor progression. The recently identified role of some macrophages as "corrupted policemen" has made them as an appealable target for anticancer therapies, leading in several cases to the reduction of tumor growth and of metastatic spread, as well as to synergistic effects when combined with antiangiogenic and chemotherapeutic agents.[33] For example, *trabectedin*, a chemotherapeutic agent that kills monocytes/macrophages, demonstrated therapeutic efficacy against tumors in mouse models.[34] The main problem in this approach is that a pan-macrophage treatment might produce important side effects, since it targets all macrophages. So *more refined therapies that only target TAMs* are urgently needed.

As for neutrophils, most of the molecules under current investigation are clinically approved drugs, whose indications generally concern inflammatory and autoimmune diseases. For example, *zileuton*, an approved drug for the treatment of inflammatory asthma, is an inhibitor of arachidonate 5-lipoxygenase (Alox5), an enzyme that generates leukotrienes (LTs). This drug also proved to reduce the formation of lung metastases in a breast cancer model and this effect seems to be due to the *block of the pro-metastatic activity of neutrophils which depends on the LT/Alox5-axis*.[12] Moreover, it is known that neutrophil mobilization from the bone marrow is regulated by a signaling pathway *via* the C-X-C chemokine receptors (CXCRs). Thus, an antagonist of CXCR1 and CXCR2, *reparixin*,[35] is currently being employed in ongoing clinical trials in cancer patients,[36] since it seems to *counteract the formation of metastases by reducing neutrophil counts*, inflammatory biomarkers and, allegedly, also the contribution of cancer stem cells to tumor dissemination.

A separate reflection should be dedicated to the use of *Granulocyte Colony Stimulating Factor (G-CSF)* and *Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)*. These factors are often administered to cancer patients to counteract chemotherapy-induced neutropenia, which might lead to severe infections. Unfortunately, recent studies demonstrated that they induce a pro-tumorigenic phenotype of neutrophils and support metastasis formation.[37] Another study showed that neutralization of G-CSF or interleukin-17 reduces the formation of lung and lymph node metastases in a mouse model of breast cancer by preventing neutrophil accumulation and their T-cell-suppressive phenotype.[38] A similar phenomenon was also observed in macrophages, because GM-CSF may act in pro-tumoral fashion by stimulating TAMs[39] and treatment with a brain-penetrant *inhibitor of CSF-1 receptor (BLZ945)* proved to be effective in a glioma xenograft model.[40] Similarly, TAM-depleting effects obtained by administration of a *monoclonal antibody that blocks the activity of macrophage colony-stimulating factor 1 (CSF-1)* produced marked clinical benefits, when combined with standard-of-care treatments in patients affected by various types of solid tumors.[41] In any case, a *particular caution* should be taken before *administering G-CSF to cancer patients* and the risk-benefit ratio should be more precisely assessed by a careful analysis of large populations. In addition, there is an urgent need for more selective therapeutic interventions which are able to prevent neutropenia-induced infections without stimulating the neutrophil or macrophage pro-metastatic character.

Finally, it is now widely accepted that anti-inflammatory agents can be profitably used together with standard anti-tumor treatments. In fact, a reduction of systemic inflammation caused by cancer, once considered only as a palliative care for symptom control, remarkably improves not only the quality of life, but also the survival rate in oncologic patients.[42] The good news is that some classical non-steroidal anti-inflammatory drugs (*NSAIDs*), such as naproxen, ibuprofen and oxaprozin, were found to *reduce neutrophil migration* by means of a mechanism that is independent of COX inhibition and PGE_2 release.[43] The direct effects of these arylpropionic NSAIDs on neutrophil behavior should inspire extensive studies aimed at the discovery of new and more specific anti-cancer drugs targeting this type of immune cells.

Summary and outlook

"The History of the World Based on Banalities" is the title of a theatre show, but it may be as well used to explain the sense of this personal viewpoint, where trivial observations are proposed to stimulate the implementation of new strategies to tackle cancer. Among the numerous possible points of intervention deriving from the above-mentioned observations, some of them are summarized in the following list of over-simplified suggestions, to be considered in combination with standard-of-care therapies and under the supervision of healthcare professionals:

1) Promotion of non-strenuous physical activity as a regulation in defense of public health.
2) Reduction of caloric intake (diet, fasting, caloric restriction mimetics).
3) Anti-IGF1/GH interventions (somatostatin analogues, pegvisomant, diet, reduced protein intake).
4) Detection of lactate as a biomarker (dogs, sensors).
5) Safety check of clinically used parenteral solutions containing lactate.
6) Development of anti-glycolytic drugs.
7) Anti-cancer immune-fortification (immunotherapy, fasting-mimicking diet, caloric restriction mimetics).
8) Development of anti-macrophage agents (trabectedin).
9) Development of anti-neutrophil agents (reparixin).
10) Safety check of Colony Stimulating Factors (G/GM-CSF) and of their risk-benefit ratio.
11) Higher employment of anti-inflammatory (anti-TAMs/TANs) drugs in cancer treatment protocols.

Of course, these are just hints for discussion, which may not necessarily encounter a universal consent in the scientific community. Anyway, cancer is such a complex disease, maybe it is even a complex collection of different diseases, whose

treatment requires a wide panel of interventions, which cannot be limited to a single therapeutic protocol. So, in order to reduce the complexity of the treatment options and, at the same time, to increase the chance of their implementation, a series of “easy” deductions and common-sense approaches are herein proposed. Let’s fly low for a while. We may be surprised by what we can see from closer distances.

Acknowledgements

I would like to express my sincere gratitude to Dr. Mario Varasi (Istituto Europeo di Oncologia – IEO, Milan, Italy) for his tireless attempts (*not always successful, I regret…*) to teach me how to handle very complex issues in a smartly simplified, target-focused, and spontaneously humoristic way.

Keywords: cancer • metabolism • heart • plants • immune cells

References:

[1] B. Vogelstein, N. Papadopoulos, V. E. Velculescu, S. Zhou, L. A. Diaz Jr., K. W. Kinzler, *Science* **2013**, *339*, 1546–1558.

[2] G. Shanmugam, *Eur. J. Cardio-Thorac. Surg.* **2006**, *29*, 925-932.

[3] O. Bergmann, R. D. Bhardwaj, S. Bernard, S. Zdunek, F. Barnabé-Heider, S. Walsh, J. Zupicich, K. Alkass, B. A. Buchholz, H. Druid, S. Jovinge, J. FrisénAuthor, *Science* **2009**, *324*, 98-102.

[4] U. E. Martinez-Outschoorn, M. Peiris-Pagés, R. G. Pestell, F. Sotgia, M. P. Lisanti, *Nat. Rev. Clin. Oncol.* **2016**, Published online 04 May 2016, doi: 10.1038/nrclinonc.2016.60.

[5] M. J. Khandekar, P. Cohen, B. M. Spiegelman, *Nat. Rev. Canc.* **2011**, *11*, 886-895.

[6] a) S. K. Denduluri, O. Idowu, Z. Wang, Z. Liao, Z. Yan, M. K. Mohammed, J. Ye, Q. Wei, J. Wang, L. Zhao, H. H. Luu, *Genes Dis.* **2015**, *2*, 13-25; b) S. Djiogue, A. H. N. Kamdje, L. Vecchio, M. J. Kipanyula, M. Farahna, Y. Aldebasi, P. F. Seke Etet, *Endocr.-Relat. Cancer* **2013**, *20*, R1-R17; c) H. Yu, T. Rohan, *J. Natl. Cancer Inst.* **2000**, *92*, 1472-1489.

[7] E. Bonavita, M. R. Galdiero, S. Jaillon, A. Mantovani, *Adv. Cancer Res.* **2015**, *128*, 141-171.

[8] S. B. Coffelt, M. D. Wellenstein, K. E. de Visser, *Nat. Rev. Cancer* **2016**, *16*, 431-446.

[9] a) Y. Han, Z. Yu, S. Wen, B. Zhang, X. Cao, X. Wang. *Breast Cancer Res. Treat.* **2012**, *131*, 483-490; b) K. Shitara, K. Matsuo, D. Takahari, T. Yokota, Y. Inaba, H. Yamaura, Y. Sato, M. Najima, T. Ura, K. Muro. *Eur. J. Cancer* **2009**, *45*, 1757-1763.

[10] A. J. Templeton, M. G. McNamara, B. Šeruga, F. E. Vera-Badillo, P. Aneja, A. Ocaña, R. Leibowitz-Amit, G. Sonpavde, J. J. Knox, B. Tran, I. F. Tannock, E. Amir. *J. Natl. Cancer Inst.* **2014**, *106*, dju124.

[11] J. Cools-Lartigue, J. Spicer, B. McDonald, S. Gowing, S. Chow, B. Giannias, F. Bourdeau, P. Kubes, L. Ferri. *J. Clin. Invest.* **2013**, *123*, 3446-3458.

[12] S. K. Wculek, I. Malanchi. *Nature* **2015**, *528*, 413-417.

[13] J. Guevara-Aguirre, P. Balasubramanian, M. Guevara-Aguirre, M. Wei, F. Madia, C. W. Cheng, D. Hwang, A. Martin-Montalvo, J. Saavedra, S. Ingles, R. de Cabo, P. Cohen, V. D. Longo. *Sci. Transl. Med.* **2011**, *3*, 70ra13.

[14] S. Wirén, C. Häggström, H. Ulmer, J. Manjer, T. Bjørge, G. Nagel, D. Johansen, G. Hallmans, A. Engeland, H. Concin, H. Jonsson, R. Selmer, S. Tretli, T. Stocks, P. Stattin. *Cancer Causes Control* **2014**, *25*, 151-159.

[15] a) S. T. Chari, C. L. Leibson, K. G. Rabe, J. Ransom, M. de Andrade, G. M. Petersen. *Gastroenterology* **2005**, *129*, 504-511; b) R. Huxley, A. Ansary-Moghaddam, A. Berrington de Gonzales, F. Barzi, M. Woodward. *Br. J. Cancer* **2005**, *92*, 2076-2083.

[16] M. Pollak. *J. Clin. Invest.* **2013**, *123*, 3693-3700.

[17] B. Lauby-Secretan, C. Scoccianti, D. Loomis, Y. Grosse, F. Bianchini, K. Straif, *N. Engl. J. Med.* **2016**, *375*, 794-798.

[18] S. C. Moore, I. M. Lee, E. Weiderpass, P. T. Campbell, J. N. Sampson, C. M. Kitahara, S. K. Keadle, H. Arem, A. Berrington de Gonzalez, P. Hartge, H. O. Adami, C. K. Blair, K. B. Borch, E. Boyd, D. P. Check, A. Fournier, N. D. Freedman, M. Gunter, M. Johannson, K. T. Khaw, M. S. Linet, N. Orsini, Y. Park, E. Riboli, K. Robien, C. Schairer, H. Sesso, M. Spriggs, R. Van Dusen, A. Wolk, C. E. Matthews, A. V. Patel, *JAMA Intern. Med.* **2016**, *176*, 816-825.

[19] S. T. Mayne, M. C. Playdon, C. L. Rock. *Nat. Rev. Clin. Oncol.* **2016**, *13*, 504-515.

[20] G. Bianchi, R. Martella, S. Ravera, C. Marini, S. Capitanio, A. Orengo, L. Emionite, C. Lavarello, A. Amaro, A. Petretto, U. Pfeffer, G. Sambuceti, V. Pistoia, L. Raffaghello, V. D. Longo *Oncotarget* **2015**, *6*, 11806-11819.

[21] R. J. Klement, M. K. Fink. *Oncogenesis* **2016**, *5*, e193.

[22] I. Rogers, P. Emmett, D. Gunnell, D. Dunger, J. Holly, ALSPAC Study Team. *Public Health Nutr.* **2006**, *9*, 359-368.

[23] a) Y. Schönbeck, H. Talma, P. van Dommelen, B. Bakker, S. E. Buitendijk, R. A. HiraSing, S. van Buuren, *Pediatr. Res.* **2013**, *73*, 371-377; b) CD Risk Factor Collaboration (NCD-RisC). *eLife* **2016**, *5*, e13410.

[24] M. E. Levine, J. A. Suarez, S. Brandhorst, P. Balasubramanian, C. W. Cheng, F. Madia, L. Fontana, M. G. Mirisola, J. Guevara-Aguirre, J. Wan, G. Passarino, B. K. Kennedy, M. Wei, P. Cohen, E. M. Crimmins, V. D. Longo. *Cell Metab.* **2014**, *19*, 407-417.

[25] a) A. J. van der Lely, J. J. Kopchick. *Neuroendocrinology* **2006**, *83*, 264-268; b) J. Divisova, I. Kuiatse, Z. Lazard, H. Weiss, F. Vreeland, D. L. Hadsell, R. Schiff, C. K. Osborne, A. V. Lee. *Breast Cancer Res. Treat.* **2006**, *98*, 315-327.

[26] a) G. Bonuccelli, A. Tsirigos, D. Whitaker-Menezes, S. Pavlides, R. G. Pestell, B. Chiavarina, P. G. Frank, N. Flomenberg, A. Howell, U. E. Martinez-Outschoorn, F. Sotgia, M. P. Lisanti. *Cell Cycle* **2010**, *9*, 3506-3514; b) F. Polet, O. Feron. *J. Intern. Med.* **2013**, 273, 156-165.

[27] a) S. W. Brooks, D. R. Moore, E. B. Marzouk, F. R. Glenn, R. M. Hallock. *Cancer Invest.* **2015**, *33*, 411-419; b) R. Gasparr, M. Santonico, C. Valentini, G. Sedda, A. Borri, F. Petrella, P. Maisonneuve, G. Pennazza, A. D'Amico, C. Di Natale, R. Paolesse, L. Spaggiari. *J. Breath Res.* **2016**, *10*, 016007.

[28] U. Yoel, J. Gopas, J. Ozer, R. Peleg, P. Shvartzman. *Isr. Med. Assoc. J.* **2015**, *17*, 567-570.

[29] J. Zhang, Y. H. Yao, B. G. Li, Q. Yang, P. Y. Zhang, H. T. Wang. *Sci. Rep.* **2015**, 5, 9800.

[30] a) C. Granchi, F. Minutolo. *ChemMedChem* **2012**, *7*, 1318-1350; b) J. R. Doherty, J. L. Cleveland. *J. Clin. Invest.* **2013**, *123*, 3685-3692; c) C. Granchi, D. Fancelli, F. Minutolo. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4915-4925; d) U. E. Martinez-Outschoorn, M. Peiris-Pagés, R. G. Pestell, F. Sotgia, M. P. Lisanti. *Nat. Rev. Clin. Oncol.* **2016**, Published online 04 May 2016, doi:10.1038/nrclinonc.2016.60.

[31] T. N. Schumacher, R. D. Schreiber. *Science*, **2015**, *348*, 69-74.

[32] a) S. Di Biase, C. Lee, S. Brandhorst, B. Manes, R. Buono, C. W. Cheng, M. Cacciottolo, A. Martin-Montalvo, R. de Cabo, M. Wei, T. E. Morgan, V. D. Longo. *Cancer Cell* **2016**, *30*, 136-146; b) F. Pietrocola, J. Pol, E. Vacchelli, S. Rao, D. P. Enot, E. E. Baracco, S. Levesque, F. Castoldi, N. Jacquelot, T. Yamazaki, L. Senovilla, G. Marino, F. Aranda, S. Durand, V. Sica, A. Chery, S. Lachkar, V. Sigl, N. Bloy, A. Buque, S. Falzoni, B. Ryffel, L. Apetoh, F. Di Virgilio, F. Madeo, M. C. Maiuri, L. Zitvogel, B. Levine, J. M. Penninger, G. Kroemer. *Cancer Cell* **2016**, *30*, 147-160.

[33] R. Noy, J. W. Pollard, *Immunity* **2014**, *41*, 49-61.

[34] G. Germano, R. Frapolli, C. Belgiovine, A. Anselmo, S. Pesce, M. Liguori, E. Erba, S. Uboldi, M. Zucchetti, F. Pasqualini, M. Nebuloni, N. van Rooijen, R. Mortarini, L. Beltrame, S. Marchini, I. Fuso Nerini, R. Sanfilippo, P. G. Casali, S. Pilotti, C. M. Galmarini, A. Anichini, A. Mantovani, M. D'Incalci, P. Allavena. *Cancer Cell.* **2013**, *23*, 249-262.

[35] R. Bertini, M. Allegretti, C. Bizzarri, A. Moriconi, M. Locati, G. Zampella, M. N. Cervellera, V. Di Cioccio, M. C. Cesta, E. Galliera, F. O. Martinez, R. Di Bitondo, G. Troiani, V. Sabbatini, G. D'Anniballe, R. Anacardio, J. C. Cutrin, B. Cavalieri, F. Mainiero, R. Strippoli, P. Villa, M. Di Girolamo, F. Martin, M. Gentile, A. Santoni, D. Corda, G. Poli, A. Mantovani, P. Ghezzi, F. Colotta. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 11791-11796.

[36] [a) US National Library of Medicine. ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT02370238 (2015); b) US National Library of Medicine. ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT02001974 (2015).]

[37] A. J. Casbon, D. Reynaud, C. Park, E. Khuc, D. D. Gan, K. Schepers, E. Passegué, Z. Werb. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, E566-E575.

[38] S. B. Coffelt, K. Kersten, C. W. Doornebal, J. Weiden, K. Vrijland, C. S. Hau, N. J. Verstegen, M. Ciampricotti, L. J. Hawinkels, J. Jonkers, K. E. de Visser. *Nature* **2015**, *522*, 345-348.

[39] S. Su, Q. Liu, J. Chen, J. Chen, F. Chen, C. He, D. Huang, W. Wu, L. Lin, W. Huang, J. Zhang, X. Cui, F. Zheng, H. Li, H. Yao, F. Su, E. Song. *Cancer Cell.* **2014**, *25*, 605-620.

[40] S. M. Pyonteck, L. Akkari, A. J. Schuhmacher, R. L. Bowman, L. Sevenich, D. F. Quail, O. C. Olson, M. L. Quick, J. T. Huse, V. Teijeiro, M. Setty, C. S. Leslie, Y. Oei, A. Pedraza, J. Zhang, C. W. Brennan, J. C. Sutton, E. C. Holland, D. Daniel, J. A. Joyce, *Nat. Med.* **2013**, *19*, 1264-1272.

[41] C. H. Ries, M. A. Cannarile, S. Hoves, J. Benz, K. Wartha, V. Runza, F. Rey-Giraud, L. P. Pradel, F. Feuerhake, I. Klaman, T. Jones, U. Jucknischke, S. Scheiblich, K. Kaluza, I. H. Gorr, A. Walz, K. Abiraj, P. A. Cassier, A. Sica, C. Gomez-Roca, K. E. de Visser, A. Italiano, C. Le Tourneau, J. P. Delord, H. Levitsky, J. Y. Blay, D. Rüttinger. *Cancer Cell* **2014**, *25*, 846-859.

[42] C. S. D. Roxburgh, D. C. McMillan. *Br. J. Canc.* **2014**, *110*, 1409-1412.

[43] M. Bertolotto, P. Contini, L. Ottonello, A. Pende, F. Dallegri, F. Montecucco. *Br. J. Pharmacol.* **2014**, *171*, 3376-3393.

Entry for the Table of Contents

Why is heart substantially immune to cancer? Why do certain dwarf populations have reduced incidence of tumors? Why do plants get cancer but no metastases? These and other trivial observations would deserve a higher consideration by the scientific community, since they might suggest innovative approaches to tackle cancer.