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► **To cite this version:**

Guido Kroemer, Jennifer L Mcquade, Miriam Merad, Fabrice André, Laurence Zitvogel. Bodywide ecological interventions on cancer. *Nature Medicine*, 2023, 29 (1), pp.59-74. 10.1038/s41591-022-02193-4 . hal-04596765

**HAL Id: hal-04596765**

**<https://hal.science/hal-04596765>**

Submitted on 4 Jun 2024

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## Perspective

# Bodywide ecological interventions on cancer

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Running title: Ecological interventions on cancer

Keywords: chemotherapy, diet, immunotherapy, lifestyle, microbiota

## **Abstract**

Historically, cancer research and therapy have focused on malignant cells and their tumor microenvironment. However, the vascular, lymphatic and nervous systems establish a long-range communication of the tumor with the host. This communication is mediated by metabolites elaborated by the host or the gut microbiota, as well by systemic neuroendocrine, pro-inflammatory and immune circuitries, all of which dictate the trajectory of malignant disease through molecularly defined biological mechanisms. Moreover, underlying conditions including aging, comorbidities and comedications have a major impact on the development, progression and therapeutic response of cancer patients. In this Perspective, we advocate in favor of a whole-body ‘ecological’ exploration of malignant disease. We surmise that accumulating knowledge on the intricate relationship between the host and the tumor will shape rational strategies for systemic, bodywide interventions that will eventually improve tumor control, as well as quality of life, in cancer patients.

## Introduction

Historically <sup>1,2</sup>, cancer was considered as a cell-autonomous disease caused by (epi)genetically unstable cells. Thus, therapies aimed at the eradication of malignant cells by cytotoxicants, ionizing irradiation or targeted agents (**Fig. 1A**). The later realization that tumors require the support by non-transformed stromal cells led to the development of anti-angiogenic therapies (**Fig. 1B**). More recently, the detection of tumor-infiltrating leukocytes and tumor-specific T cells gave rise to the concepts of immunosurveillance and immunotherapy (**Fig. 1C**). At this stage, oncology has been developing an ever more sophisticated arsenal of spatially resolved multi-omics technologies to explore the organization of the tumor microenvironment (TME) around (epi)genetically heterogeneous cancer cells <sup>3,4</sup>. However, the vision of cancer has remained tumor-centric.

Here, we advocate in favor of an ‘ecological’, bodywide view of malignant disease (**Fig. 1D**) that is conditioned by the interaction of multiple different cell types within and outside of the tumor embedded in systemic metabolic, neuroendocrine, inflammatory or immune circuitries, and profoundly influenced by aging, comorbidities and comedications <sup>5,6</sup>. Thus, we will put forth the viewpoint that cancer should not only be treated by agents targeting the neoplastic cells themselves or the TME but also by interventions on the bodywide ecosystem.

The ecological exploration of cancer transcends the tumor-centric characterization of malignant cells (genomics, epigenomics, heterogeneity...) and that of the tumor microenvironment (TME) with its stromal, inflammatory and immune elements. Such long-distance effects are possible due to the constant communication between the tumor and the rest of the body via the vascular, lymphatic and nervous systems. These interactions are mediated by metabolites produced by the host or the gut microbiota, neuroendocrine factors including neurotransmitters, neuropeptides and hormones, pro-inflammatory and pro-fibrotic factors and cells and their endogenous inhibitors, circulating immune effectors, regulatory cells, immunostimulators and immunosuppressants, as well as iatrogenic factors including drugs used for the treatment of non-malignant diseases. We consider that these factors configure the most relevant facets of the bodywide ecosystem with respect to oncogenesis and tumor progression.

In this Perspective, we will discuss how cancer is impacted by the ecosystem stratified into four different but interdependent layers operating at the systemic level, namely, (i) metabolism, (ii) neuroendocrine circuitries, (iii) inflammation and (iv) immunity. We will summarize preclinical and clinical evidence supporting the importance of these strata for the pathogenesis and treatment of malignant disease.

## Systemic metabolism

Malignant cells differ from their normal counterparts with respect to their metabolic features, resulting in enhanced nutrient uptake and anabolic reactions that enable cell growth and division, as well as subtle alterations that trigger (epi)genomic instability and favor evasion from immunosurveillance <sup>7</sup>. This realization has triggered the search for drugs that would inhibit specific facets of cancer cell metabolism without major side effects on normal cells. However, oncometabolism thus far has been rarely targeted at the clinical level, with the notable exceptions of antimetabolite chemotherapies that inhibit the biosynthesis of DNA precursor molecules and inhibitors of mutant isocitrate dehydrogenases 1 and 2 (IDH1, 2) for the treatment of acute myeloid leukemia and cholangiocarcinoma bearing activating mutations of IDH1 or IDH2 <sup>8</sup>. Moreover, the growing awareness of the importance of immunometabolism, i.e., metabolic specificities of distinct myeloid and lymphoid cells in the TME, has not yet impacted the clinical routine <sup>9</sup>.

**Systemic metabolism in tumor biology.** The role of systemic, body-wide metabolism is well-established in carcinogenesis (**Fig. 2A**). Both the quantity and quality of nutrients can contribute to the risk of developing malignant disease. Thus, obesity is an established risk factor for 13 different malignancies and also associated with worse prognosis in many cancers <sup>10,11</sup>. Mechanistically, excessive nutrients (amino acids, glucose, lipids) and growth factors (such as insulin and insulin-like growth factor-1, IGF1) suppress autophagy and precipitate premature tissue aging <sup>12</sup>. Obesity can reprogram malignant cells towards enhanced lipid uptake, which results in reduced immunosurveillance by cytotoxic T lymphocytes <sup>13</sup>. Adipose tissue-derived estrogens, adipokines and inflammatory mediators contribute to oncogenesis and tumor progression <sup>14</sup>. Obesity-associated hyperleptinemia and hypoghrelinemia may explain excessive angiogenesis and fibrotic responses <sup>15</sup>. Obesity also compromises the efficacy of PD-1-based immunotherapies in renal cancer patients <sup>16</sup>. Interestingly, obesity has been paradoxically associated with improved response to immunotherapy in melanoma and non-small cell lung cancer, an effect that may in part be due to the functional immune exhaustion induced by obesity rendering a target for immune checkpoint inhibitor reinvigoration and/or interactions between host and tumor metabolism <sup>17-19</sup>.

Red meat is associated with distal colon carcinogenesis through mechanisms that may involve changes in the microbiota, as well as alkylating DNA damage by N-nitroso-compounds, which are metabolic products of heme iron or nitrites/nitrates <sup>20</sup>. The hepatocarcinogenic effects of alcohol and its metabolites are explained by mutagenic oxidative stress, epigenomic alterations, endoplasmic reticulum stress, gut leak and dysbiosis, resulting in enhanced hepatocyte turnover and inflammation <sup>21</sup>. Conversely, coffee consumption significantly reduces risk of hepatocellular carcinoma likely due to the

induction of oncosuppressive autophagy<sup>22</sup>. However, the impact of specific food items on cancer has thus only been demonstrated within the limits of epidemiological associations calling for future interventional trials.

Of note, cancers can influence whole body metabolism even at early stages of tumor development, for instance due to adrenergic stress affecting the ileum, resulting in histological signs of inflammation and shifts of the intestinal microbiota<sup>23</sup>. At later stages, cancer affects general metabolism, likely through pro-inflammatory signaling, culminating in cachexia<sup>24</sup>. Thus, whole-body mechanisms and cancer mutually influence each other.

**Diagnostic and prognostic implications.** Serum metabolomics hold great potential for use in the diagnosis of malignancy. Nuclear magnetic resonance metabolomics can be applied to whole blood to diagnose neoplasia in a mixed population of patients with nonspecific symptoms<sup>25</sup>. Technological advances in mass spectrometric metabolomics have refined the analysis of serum metabolites to accurately distinguish early-stage carcinoma-bearing patients from healthy controls (with both sensitivity and specificity >80%) and to identify the tissue of origin of the cancer<sup>26</sup>. Although shifts in the microbiota (which accounts for a major fraction of mass-spectrometric peaks in the circulating metabolome)<sup>27</sup> are often similar in malignant and non-cancerous pathologies<sup>28</sup>, the metabolome of oncological patients undergoes disease-specific alterations. In addition, plasma metabolomics has helped to identify biomarkers (in particular, a decrease in the fatty acids  $\alpha$ -linolenic acid, linoleic acid and palmitic acid) that predict the progression of precancerous gastric lesions to carcinoma<sup>29</sup>. 2-hydroxyglutarate can be monitored in the plasma to detect cancers with mutant IDH1/2<sup>30</sup>. High levels of short chain fatty acids (acetate, propionate and butyrate, which are formed in the gut by bacterial fermentation of dietary fibers) have been associated with favorable responses to immunotherapy across several studies<sup>31</sup>. High plasma levels of trimethylamine N-oxide, a microbial metabolite, are associated with favorable prognosis in triple-negative breast cancer (TNBC) patients, and its systemic administration to mice reduces TNBC growth in mice, synergizing with PD-1 blockade<sup>32</sup>. These findings underscore the potential diagnostic and prognostic importance of the circulating metabolome, and the need for further development and clinical validation of metabolomics in cancer detection. Moreover, standardization of methods for measuring absolute (rather than relative) metabolite concentrations is necessary to facilitate cross-cohort comparisons.

**Whole-body metabolic interventions.** Dietary interventions are given consideration in primary or secondary prevention, as well as potential adjunct therapies<sup>33,34</sup>. The most solid evidence obtained in phase 3 trials indicates that nicotinamide, a precursor of vitamin B3, has prophylactic effects for the prevention of non-melanoma skin cancers<sup>35</sup>. Although vitamin B3 precursors have an excellent safety profile and actually increase healthspan in mice<sup>36</sup>, this has not led to the FDA/EMA approval of vitamin B3 as a chemopreventive agent. Similarly, vitamin D supplementation failed to reduce overall cancer

incidence but did diminish the incidence of advanced (metastatic or fatal) cancer in a large randomized trial<sup>37</sup>. Vitamin D specifically reduced the risk of *in situ* ductal breast carcinoma<sup>38</sup>, though without a subsequent FDA/EMA approval for this indication.

Based on preclinical or preliminary clinical evidence, multiple clinical trials are exploring novel nutritional strategies for the prevention or treatment of cancer (**Table 1**). Promising general nutritional interventions on cancer include hypocaloric ‘fasting mimicking diets’, ketogenic diets in which extremely low carbohydrate intake drives compensatory ketogenesis, as well as the extra supply of dietary fibers<sup>34</sup>. In addition, preclinical experimentation has led to the identification of a series of chemically defined food ingredients, all of which are small molecules and can be supplemented as drug-like compounds in clinical trials. Of note, due to the lack of compliance associated with major dietary interventions, there is a tendency to replace dietary changes by synthetic metabolites. This applies to ketogenic diet, which, in mice, can be replaced by direct oral supplementation of the major ketone body, 3-hydroxybutyrate<sup>39,40</sup>, as well as to dietary fibers that could be replaced by the administration of the short-chain fatty acid butyrate, though these strategies will require clinical testing<sup>41,42</sup>. Another major tendency regards the antineoplastic mode of action of nutrition-related small molecules, most of which do not mediate direct effects against malignant cells but rather stimulate immunosurveillance<sup>34</sup>. Ongoing and future trials must determine which among these metabolites are clinically useful (**Table 1**). Moreover, it will be interesting to enrich the pipeline of possible anticancer metabolites by exhaustive mass spectrometric metabolomics designed to identify new metabolites associated with favorable cancer prognosis or complete therapeutic responses. Finally, the development of drugs acting on metabolic pathways including so-called ‘caloric restriction mimetics’ is underway and might enter clinical evaluation soon<sup>8,43</sup>.

Epidemiological studies indicate that lipophilic statins (such as atorvastatin, lovastatin, rosuvastatin and simvastatin) diminish the risk of lethal prostate cancer<sup>44</sup> and hepatocellular carcinoma, irrespective of its etiology (hepatitis B or C virus infection, alcohol abuse and non-alcoholic steatohepatitis)<sup>45</sup>, yet fail to unravel a general diminution of cancer incidence among statin users. In breast cancer patients, post-diagnostic statin use is associated with improved recurrence free, overall and cancer-specific survival<sup>46</sup>. Moreover, in patients with renal or non-small cell lung carcinoma, statin administration is associated with improved therapeutic responses to PD-1 blockade<sup>47,48</sup>. These statin effects might involve direct cytotoxic effects<sup>49</sup>, immunogenic stress affecting malignant cells<sup>50</sup> or the depletion of oxidized low-density lipoprotein (ox-LDL), which is immunosuppressive<sup>51</sup>. Numerous trials are evaluating the anticancer effects of statins (**Table 1**).

## Neuroendocrine factors

Gender-specific tumors often are under the trophic support of sex hormones such as estrogens for hormone receptor-positive mammary carcinoma, ovarian and endometrial cancer, as well as androgens for prostate carcinoma. These cancer types usually respond to hormone receptor antagonists (i.e., antiestrogens and antiandrogens), as well as hormone synthesis inhibitors (i.e., aromatase inhibitors for estrogens, CYP17A1 inhibitors or gonadotropin-releasing hormone [GnRH] antagonists for androgen synthesis) before they become hormone-independent and progress<sup>52,53</sup>. Similarly, a fraction of neuroendocrine cancer transiently responds to somatostatin analogues<sup>54</sup>. The therapeutic action and later failure of such (neuro)endocrine treatments have usually been explained by cell-intrinsic alterations in malignant cells. However, it should be noted that, in a model of hormone-induced breast cancer, chemoprophylaxis mediated by the antiestrogen tamoxifen is efficient in immunocompetent mice but completely fails in immunodeficient *Rag2<sup>-/-</sup>Il2rg<sup>-/-</sup>* animals<sup>55</sup>. Similarly, androgen deprivation therapy (ADT) against prostate cancer using the GnRH antagonist degarelix improves thymic output in patients and loses therapeutic efficacy in athymic mice<sup>56</sup>. The combination of ADT and the antiandrogen enzalutamide also improves effector T cell function, thus sensitizing to immune checkpoint blockade, likely by reactivating immune-relevant genes such as IFN $\gamma$ , which is directly repressed by androgen receptor in T cells<sup>57</sup>. Moreover, in mice and patients with castration-resistant prostate cancer emerges when gut bacteria start producing androgens<sup>58</sup>. These findings strongly suggest that the cell-autonomous view of therapeutic (un)responsiveness to hormone therapy is a short circuit. Moreover, hormone therapy may act in an unsuspected fashion, as this is the case for BRAF/MEK-targeted therapy of melanoma, which works less efficiently in males than in females (in human and mouse) unless the treatment is combined with androgen receptor blockade (in mice)<sup>59</sup>.

Malignant cells can release neurotrophic proteins such as brain-derived neurotrophic factor, glial cell-derived neurotrophic factor and nerve growth factor, as well as axon-guidance molecules such as ephrin B1, thus recruiting neural progenitors into the TME to facilitate their differentiation to adrenergic phenotypes or reprogramming established nerves towards adrenergic functions<sup>60,61</sup>. The density of autonomic nerve fibers innervating cancers has a negative prognostic impact in patients with hepatocellular carcinoma<sup>62</sup> or prostate cancer<sup>63</sup>, *inter alia*. Nonetheless, the interest of anatomical pathologists in nerve fibers present within tumors has long been focused on the phenomenon of perineural invasion as a mechanism of metastatic spread, hence adopting a purely tumor-centric view<sup>64</sup>, colliding with the observation that modulation of the sensory, sympathetic and parasympathetic systems has major effects on tumor progression<sup>65</sup>. Indeed, over the last few years, the functional impact of autonomic innervation of cancers, as well as that of a myriad of neuroendocrine factors including neurotransmitters (such as catecholamines and gamma-aminobutyric acid, GABA), neuropeptides, ‘tissue hormones’ (such as adiponectin and leptin) and classical hormones (produced by endocrine organs) on cancer cells and TME have been documented<sup>66,67</sup>. The most compelling evidence in favor



of an ‘ecological’ role of such factors concerns stress hormones such as catecholamines and glucocorticoids that may constitute actionable targets for clinical intervention (**Table 1**).

**Neuropeptides.** Multiple human malignancies overexpress neuropeptide Y (NPY) that mediates autocrine and paracrine effects <sup>67</sup>. For example, hypoxic Ewing osteosarcoma cells produce NPY that induces polyploidization with consequent chromosomal instability <sup>68</sup>. Human colon adenocarcinoma cells can ectopically produce NPY that acts on endothelial cells to stimulate angiogenesis <sup>69</sup>. Thus, malignant cells can ectopically produce neuropeptides to accelerate tumor progression. Of note, psychological depression may enhance NPY secretion via sympathetic signaling, perhaps explaining correlations between depression, local NPY production and poor prognosis in prostate cancer patients <sup>70</sup>. Several other neuropeptides (such as substance P, neurotensin, orexin/hypocretin etc.) are present in tumors, mediating mostly pro-oncogenic effects. Some of these factors, in particular substance P, may mediate cancer-associated behavioral changes (e.g., stress, anxiety and depression) when they reach the central nervous system <sup>67</sup>.

**Neurotransmitters.** Malignant cells can produce neurotransmitters, as shown for human triple-negative breast cancer cell lines and pancreatic tumors in mice that produce 5-hydroxytryptamine (5-HT, also called serotonin), which acts in an autocrine fashion to promote growth <sup>71,72</sup>. 5-HT also stimulates pro-tumorigenic inflammasome activation (via the activation of the 5-HT receptor 3A, HTR3A, on macrophages) in colorectal cancer progression, meaning that the inhibition of the 5-HT synthesizing enzyme tryptophan hydroxylase 1 or treatment with an HTR3A antagonist counteracts the process <sup>73</sup>. Castration-resistant prostate cancers as well as lung adenocarcinomas express glutamate decarboxylase 1 (GAD1), the rate limiting enzyme for the production of  $\gamma$ -aminobutyric acid (GABA) <sup>74,75</sup>. In patients with lung or colon adenocarcinoma, high intratumoral GABA levels correlate with poor overall survival <sup>76</sup>. In mice, malignant cell-derived GABA favors a paucity of the T cell infiltrates. Inhibition of the GABA generating enzyme GAT1 with 3-mercaptopropionic acid and the GABA<sub>B</sub> receptor antagonist 2-hydroxy-saclofen both restore the efficacy of PD-1 blockade against lung cancer in preclinical models <sup>76</sup>. It should be noted that an endogenous allosteric activator of the GABA<sub>A</sub> receptor, diazepam binding inhibitor (DBI), which also acts as an appetite stimulator, loses its homeostatic role in advanced cancer patients <sup>77</sup>. Although, the tumor-modulatory role of DBI remains putative, the use of benzodiazepines, which compete with DBI for GABA<sub>A</sub> receptor binding, is linked to a dose-dependent increase in the risk of developing cancer <sup>78</sup>. However, this effect may be restricted to specific benzodiazepines (such as clonazepam and zolpidem) and specific cancer types <sup>79,80</sup>.

**Tissue hormones.** Leptin, an appetite inhibitor produced by adipocytes, loses its homeostatic function in obesity, which is paradoxically associated with hyperleptinemia. In breast cancer, local leptin production is a negative prognostic feature related to macrophage infiltration <sup>81,82</sup>. Moreover, the

sexually dimorphic puberty-associated decline in adiponectin levels (produced by adipocytes), which is caused by an increase in testosterone levels, reportedly accounts for the enhanced susceptibility of males to develop hepatocellular carcinoma<sup>83</sup>. The obesity-associated raise in IGF1 levels (which is secreted by hepatocytes) may also be cancer-relevant because pharmacological blockade of IGF1R with picropodophyllin or linsitinib improves anticancer immunosurveillance by stimulating autophagy in cancer cells<sup>84</sup>. In a preclinical model of prostate cancer, short chain fatty acids generated in the gut caused an increase in circulating and local IGF1, which in turn favored tumor progression<sup>85</sup>. Although small molecule IGF1R antagonists have failed in previous trials, a monoclonal antibody neutralizing IGF1 and IGF2 is now being evaluated in the clinics (**Table 1**).

**Glucocorticoids.** The immunosuppressive effects of glucocorticoids strongly affect cancer immunosurveillance. Thus, in patients with non-small cell lung cancer or other solid cancers treated with immune checkpoint inhibitors, synthetic corticosteroid use negatively impacts clinical response and outcomes<sup>86,87</sup>. In mice, endogenous (i.e., stress induced) or exogenous glucocorticoids suppress anticancer immunosurveillance through the induction of the transcription factor TSC22D3 on dendritic cells. In patients with gastric, colorectal and lung cancer, close correlations were found among negative mood, plasma cortisol levels and TSC22D3 expression in circulating leukocytes, and TSC22D3 expression in the tumor was also associated with worse prognosis<sup>88</sup>. In addition, activation of glucocorticoids receptor (GR) directly suppresses the expression of PD-L1 and MHC-I on pancreatic cancer cells, reflecting an inverse correlation between the expression of GR and that of PD-L1 and MHC-I in pancreatic cancer patients<sup>89</sup>. Administration of the GR antagonist mifepristone improves immunosurveillance in stressed mice<sup>88</sup>. Although the clinical evaluation of mifepristone or more specific GR antagonists for oncological indications is still elusive, there is a debate on restricting the currently widespread use of corticosteroids for prevention of chemotherapy induced nausea and vomiting<sup>90</sup>.

**Antagonists of adrenergic  $\beta$ -receptors.**  $\beta$ -blockers are widely used for the management of anxiety, hypertension and cardiac arrhythmia. Observational studies indicate that the use of  $\beta$ -blockers (especially those that are non-specific, blocking several different  $\beta$ -receptor subtypes) is linked to a reduction in overall cancer mortality<sup>91</sup>, as well as to an ameliorated outcome of cancer treatments. Thus, non-specific  $\beta$ -blockade at the time of radical prostatectomy is associated with less treatment initiation for cancer recurrence<sup>92</sup>. Moreover, early data suggests that pan- $\beta$ -blockers may favorably impact outcomes in metastatic melanoma patients treated with immunotherapy<sup>93</sup>. In mouse models of breast, ovarian and prostate cancer, stimulation of the parasympathetic nervous system or surgical or pharmacological ablation of sympathetic nerves reduces tumorigenesis<sup>94-96</sup>. In such models, angiogenesis is driven by adrenergic receptor  $\beta$ 2 on endothelial cells<sup>97,98</sup>. Of note, in patients with spinal cord injury, the incidence

of prostate cancer is reduced, apparently validating the findings obtained by preclinical denervation experiments<sup>99</sup>. In mice,  $\beta$ -blockade reduces the tumor-induced stress ileopathy, slows down cancer progression<sup>23</sup>, and improves T cell-mediated cancer immunosurveillance<sup>100</sup>. Randomized clinical trials revealed that perioperative  $\beta$ -adrenergic blockade, alone or together with COX2 inhibition, improved biomarkers of metastasis in patients with breast or colorectal cancer<sup>101,102</sup>. These findings support the notion that stress hormones generally play a pro-tumorigenic role, which may be related to their pro-angiogenic and immunosuppressive effects.

In sum, it appears that multiple neuroendocrine factors impact carcinogenesis, tumor progression and therapeutic responses (**Fig. 2B**). Future research must determine which among these factors are the most salient ones to explain the established adverse effects of depression and anxiety on tumor prognosis<sup>103-105</sup>.

## **Systemic inflammation**

Chronic inflammation is a major driver of both aging ('inflammaging') and cancer ('the wound that never heals')<sup>5,106</sup>. In tumors, inflammation is spurred by local factors such as the accumulation of senescent cells with their characteristic pro-inflammatory secretome (the senescence-associated secretory phenotype, SASP), genetically unstable (pre)malignant cells that activate their DNA damage sensors to produce type-1 interferons or their inflammasomes to produce IL1 $\beta$ , which in turn promotes the recruitment of myeloid cells and in particular monocytes, macrophages and neutrophils. Local microbiota (e.g., in colorectal and lung cancer) may contribute to tumorigenesis via the stimulation of pattern recognition receptors including specific Toll-like receptors (TLRs) expressed on innate immune cells such as myeloid cells and NK cells inducing the release of protumorigenic inflammatory molecules<sup>107</sup>. Senescent and innate immune cells locally produce immunosuppressive and profibrotic cytokines (such as interleukin-6 [IL-6], IL-8, and transforming growth factor- $\beta$ , TGF- $\beta$ ), which shape the composition of the TME and exert direct trophic effects on cancer cells, eventually favoring their malignant behavior<sup>108,109</sup>. Thus, IL-6 can act as an autocrine survival factor, especially in cancer cells with chromosomal instability activating the cGAS/STING pathway<sup>110</sup>. However, such proinflammatory factors can also be detected at the systemic level. High IL-6 levels indicate poor prognosis in stage II-III colorectal cancer patients<sup>111</sup> and advanced non-small cell lung cancer<sup>112</sup>. Similarly, circulating IL-8 correlates with enhanced tumor infiltration by neutrophils and resistance to immune checkpoint inhibitors in several different malignancies<sup>113,114</sup>. Thus, inflammation transcends the local level. Although inflammation occurs within tumor lesions, it also promotes a systemic response which contributes to modulating tumor growth.

**Lifestyle factors.** Several habits have strong proinflammatory effect. Such adverse lifestyle factors include hypercaloric nutrition, coupled to the exaggerated ingestion of carbohydrates (in particular fructose causing carbotoxicity), and fat (in particular saturated *trans*-fatty acids eliciting lipotoxicity), as well as to sedentarity, have strong proinflammatory effects <sup>115</sup>. This involves a combination of systemic factors including excessive levels of pro-inflammatory hormones (insulin, IGF1, leptin), circulating cytokines (IL-1 $\beta$ , IL-6, IL-8), intestinal dysbiosis, as well as lack of exercise-induced factors (exerkines including myokines produced by the skeleton muscle) <sup>116</sup>. Excessive adiposity also drives tumorigenesis via systemic inflammation <sup>117</sup>. Altogether, these factors explain (in part) the cancerogenic effects of the prevalent Western lifestyle.

**Aberrant hematopoiesis.** Clonal hematopoiesis of indetermined potential (CHIP) results from the aging-associated genomic instability including loss-of-function modifications (most commonly in the genes *Tet2*, *Dnmt3a* and *Asx11*) which results in the potentially pathogenic expansion of myeloid progenitor cells with the consequent positive selection of preleukemic cells in the periphery. In addition to conferring an enhanced risk of acute myeloid leukemia, some of the most frequent CHIP-associated mutations in epigenomic modifiers favor systemic inflammation, precipitate atherosclerosis and increase the risk of developing solid tumors. In patients with non-hematopoietic cancers, the presence of CHIP has a negative prognostic impact <sup>118</sup>. Recent evidence indicates an enhanced frequency of CHIP in patients with a family history of lung cancer and that the mutational spectrum of CHIP is influenced by both genetic and environmental factors, in particular smoking <sup>119</sup>. Even outside of this age-related context, aberrant myelopoiesis driven by inflammation can increase the risk of tumor progression by immunosuppression affecting metastatic niches <sup>120</sup>.

**Microbiota.** The integrity of the intestinal barrier requires an equilibrated gut microbiota (eubiosis) and is fundamental for the avoidance of local and systemic inflammation, yet can be perturbed by Western style diet, ultraprocessed food and a deficit in fibers leading to an imbalance of the microflora (dysbiosis) <sup>6,121</sup>. The intestinal microbiota is composed of bacteria with anti-inflammatory properties as well as pro-inflammatory microbes, meaning that their relative abundance determines the inflammatory tonus throughout the organism <sup>122</sup>. For example, *Akkermansia muciniphila* produces a protein acting as a TLR2 agonist <sup>123</sup>, as well as a specific phospholipid acting as a mixed agonist on the TLR1/TLR2 heterodimer <sup>124</sup>, that both modulate the inflammatory tonus. Oral administration of *A. muciniphila* elevates the ileal concentrations of several anti-inflammatory metabolites (such as spermidine, short-chain fatty acids and 2-hydroxybutyrate) <sup>125</sup>, dampens intestinal, hepatic and systemic inflammation <sup>126</sup>, reduces obesity and diabetes in clinical trials <sup>127</sup> and improves anticancer immune responses in mice <sup>121</sup>. Accordingly, an optimal abundance of *A. muciniphila* in the gut predicts the success of immune checkpoint inhibition in patients with non-small cell lung cancer or melanoma <sup>128,129</sup>. Of note, host-derived lactate provides

trophic support to *A. muciniphila*<sup>130</sup>, likely explaining why this bacterium is more abundant in athletes and expands in response to exercise in mice and human<sup>131,132</sup>. Another example is provided by *Ruminococcaceae*, the abundance of which is correlated with dietary fiber consumption and that are associated with favorable response in melanoma immunotherapy<sup>133</sup>.

Thus, lifestyle determines the composition of the microbiota, which in turn affects the anticancer immune response.

**Experimental anti-inflammatory treatments.** In mice, IL1 $\beta$ , IL-6, IL-8 and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) blockade can enhance tumor response to checkpoint blockade. IL1 $\beta$  blockade improves immunosurveillance of breast and renal cancer, thus synergizing with PD-1 blockade and the tyrosine kinase inhibitor cabozantinib, respectively<sup>134,135</sup>. IL-6 blockade increases T cell infiltration while reducing the accumulation of myeloid progenitors and macrophages in melanoma lesions treated with CTLA blockade<sup>136</sup>. Knockout of IL-6 ameliorates the outcome of immunogenic chemotherapy and PD-1 blockade in mice with BCR-ABL<sup>+</sup> B-cell acute lymphoblastic leukemia<sup>137</sup>. In combination with immune checkpoint blockade, genetic deletion or pharmacological blockade of IL-8 delays the onset of prostate cancer castration resistance<sup>138</sup>. Moreover, the systemic neutralization of TNF $\alpha$  improves the outcome of dual CTLA-4/PD-1 blockade against melanoma in preclinical models<sup>139</sup>. Promising signals have been obtained in favor of the triple neutralization of CTLA-4, PD-1 and TNF in advanced melanoma patients as well<sup>140</sup>.

Chemical-genetic removal of pro-inflammatory senescent cells (in *p16-3MR*-transgenic mice in which p16<sup>INK4a</sup>-positive senescent cells can be eliminated upon treatment with ganciclovir) reduces the side effects of doxorubicin-based chemotherapy while improving its efficacy and reducing relapse rates<sup>141</sup>. Some drugs, in particular BCL2-targeted agents and cardiac glycosides also mediate senolysis, i.e., the selective destruction of senescent cells. The BCL2 inhibitor venetoclax improves anticancer immunity stimulated by PD-1 blockade<sup>142</sup>. Similarly, cardiac glycosides synergize with chemotherapeutic agents in mice<sup>143,144</sup>. Such effects may involve the direct elimination of senescent cancer cells<sup>143</sup>, indirect T lymphocyte-mediated effects secondary to the reversal of senescence-mediated immunosuppression<sup>144</sup> or the induction of immunogenic stress affecting malignant cells<sup>145</sup>. Importantly, the use of cardiac glycosides is associated with improved overall survival of patients with breast, colorectal, head and neck and hepatocellular carcinoma<sup>145</sup>, as well as with a reduced risk of developing prostate cancer<sup>146</sup>.

These examples demonstrate the theoretical possibility of targeting distinct inflammatory pathways for oncological therapy.

**Anti-inflammatory drugs in cancer epidemiology and clinical trials.** On a quantitative scale, the widely used non-steroidal anti-inflammatory drug (NSAID) acetylsalicylic acid (ASA, best known as aspirin) is possibly the most effective cancer-preventive drug to date. In observational studies, the long-

term, decade-long use of ASA reduces the probability to develop malignant disease by ~10%, with even stronger protective associations for cancers affecting the digestive tract (with a ~30% reduction of gastric and colorectal cancers)<sup>147,148</sup>. ASA also diminishes the risk of hepatocellular carcinoma irrespective of its etiology<sup>149</sup> and reduces breast cancer-specific death and risk of recurrence/metastasis<sup>150</sup>. Continued use of ASA before and after diagnosis is associated with reduced mortality from colorectal cancer<sup>151</sup>. However, results from a Phase 3 trial indicate that the use of ASA in elderly patients (>70 years) is counterproductive and even increases the risk of lethal cancer.<sup>152</sup>

NSAIDs other than ASA reduce the frequency of proximal colon cancers and improve their prognosis<sup>153</sup>. Thus, randomized controlled trials confirmed the capacity of celecoxib (an inhibitor of cyclooxygenase-2, COX2) to reduce polyp incidence in patients with familial adenomatous polyposis, as well as in patients that already undergone the resection of a sporadic adenomatous polyp, though at the cost of cardiovascular toxicity<sup>153-155</sup>. The spectrum of action of ASA appears wider than that of celecoxib, perhaps because ASA is not a mere COX2 inhibitor but also acts to stimulate autophagy and to improve cancer immunosurveillance in mice<sup>156,157</sup>. Indeed, the COX2 inhibitor acetaminophen (paracetamol) interferes with the efficacy of ICIs in mice, and its presence in plasma during treatment initiation correlates with poor outcome of immunotherapy in cancer patients<sup>158</sup>. In sharp contrast, daily ASA use is associated with more favorable outcomes in NSCLC patients treated with PD-L1 blocking antibodies<sup>159</sup>.

Antihistamines acting on histamine receptor 1 stimulate the efficacy of ICI targeting CTLA-4 or PD-1 in mouse models, likely by preventing the histamine-induced polarization of macrophages to an M2-like immunosuppressive phenotype with upregulation of the immune checkpoint VISTA.<sup>160</sup> This may be clinically relevant because the use of specific antihistamines is associated overall survival of ovarian cancer patients<sup>161</sup> and with improved outcome of immunotherapy in a pan-cancer analysis.<sup>162</sup> Moreover, circulating histamine levels negatively correlate with clinical responses to PD-1 blockade.<sup>160</sup>

Another anti-inflammatory drug, the IL-1 $\beta$  blocking antibody canakinumab can reduce lung cancer development. In a Phase 3 clinical trial designed to reduce atherosclerosis in patients with myocardial infarction and high levels of the inflammatory biomarker C-reactive protein (CRP), canakinumab administration diminished the incidence of lung cancer, coupled to reduced circulating CRP and IL-6 levels, which are risk factors for lung cancer development<sup>163,164</sup>. However, canakinumab subsequently failed in a first series of randomized trials designed to evaluate its efficacy against established lung cancers<sup>165</sup>, suggesting that IL-1 $\beta$  blockade may prevent lung cancer inception but has little effect on cancer treatment. Nonetheless, canakinumab is still being tested for its capacity to improve lung cancer immunotherapy (**Table 1**).

In summary, there is abundant evidence that systemic inflammation affects the risk of cancer morbidity and mortality (**Fig. 2C**), offering novel prospective targets for clinical intervention.

## Systemic immunity

The immune conjecture, i.e., the density, composition, functional state and spatial organization of tumor-infiltrating myeloid and lymphoid cells, is now considered as one of the strongest prognostic and predictive biomarkers for cancer outcomes<sup>166,167</sup>. High dimensional profiling analysis of human cancer lesions have enabled the identification of novel biomarkers and immune therapeutic targets<sup>168</sup>. Although this tumor-centric approach has yielded a considerable amount of information, it does not account for all facets of tumor immunology (**Fig. 2D**). For example, immune checkpoint inhibitors (ICIs) are more efficient when injected intravenously than when they are administered locally<sup>169</sup>, illustrating the preponderance of their systemic over local effects.

**Blood immunomonitoring.** The investigation of circulating immune cells by high-dimensional cytometry or single-cell RNAseq combined with single-cell TCR sequencing yields useful information for patient risk stratification. Thus, relative blood CD8<sup>+</sup> counts anticorrelate with the risk of future development of lung or breast cancer, while relative counts of FOXP3<sup>+</sup> regulatory T cells (Tregs) indicate an elevated lung cancer risk<sup>170</sup>. In human melanoma patients, expression of PDL-1 and CD95 on blood CD8<sup>+</sup> and CD4<sup>+</sup> T cells, respectively, are associated with poor prognosis<sup>171</sup>, while circulating and intratumoral T cells with the same T cell receptor (TCR) clonotypes shared gene signatures of effector functions<sup>172</sup>. Importantly, the single-cell transcriptome of blood T cells can inform, at least in part, on the functional state of their tumor-infiltrating counterparts<sup>172</sup>. In patients with advanced urothelial carcinoma, circulating neoantigen-reactive CD8<sup>+</sup> T cells with a CD39<sup>+</sup>PD1<sup>+</sup> Ki67<sup>+</sup> phenotype expand within 3 weeks in patients responding to PD-L1 blockade<sup>173</sup>, while circulating follicular T helper cells predict clinical responses to neoadjuvant pembrolizumab<sup>174</sup>. In oral cancer patients undergoing neoadjuvant immunotherapy (targeting PD-1 or PD-1 plus CTLA4) for 4 weeks, the frequency of activated blood CD8<sup>+</sup> T cells, notably PD-1<sup>+</sup> KLRG1<sup>-</sup> T cells, is robustly associated with intra-tumoral pathological responses, and similar T cell clonotypes expand in blood and tumor<sup>175</sup>. In melanoma patients under PD-1 blockade, the disappearance of tumor antigen (e.g., NY-ESO-1 or Melan-A)-reactive T cells from circulation within 6 to 9 weeks correlates with positive clinical outcome<sup>176</sup>. These examples reflect the fact that tumor antigen-specific T cells circulate in peripheral blood before they attain the tumor, establishing the importance of systemic immune responses. Moreover, they open the perspective to use sophisticated immunomonitoring methods on circulating leukocytes including functional in vitro assays to obtain insights on the anticancer immune response.

**Cross-reactivities and bystander responses.** The T cell receptor repertoire, as well as the clonotype-dependent functional properties and tissue localization of each T lymphocyte, reflects the individual's

life history of thymic or peripheral self-tolerization, exposure to commensals and pathogens, as well as cross-reactive autoimmune responses. This has wide-reaching practical implications. In several instances, pre-existing or acquired autoimmunity has a protective effect against specific cancers, as this has been exemplified by rheumatoid arthritis, Hashimoto thyroiditis and vitiligo, which are associated with a reduced frequency, as well as a better prognosis, of mammary carcinoma, thyroid cancer and melanoma, respectively<sup>177</sup>. Mice with autoimmune primary biliary cholangitis are protected against the progression of cholangiocarcinoma and shared clonotypes are found among CD8<sup>+</sup> T cells infiltrating the inflamed liver and the tumor as a proof of cross-reactivity<sup>178</sup>. In addition, T cell receptors specific for antigens from commensal bacteria can cross-react with tumor-associated antigens, as this has been documented for both human and mouse<sup>179</sup>. In cancer patients, the presence of such cross-reactive antigens in the gut and in the tumor correlates with clinical responses to immunotherapy<sup>180</sup>. Moreover, T cells may recognize bacterial peptides that are presented on MHC-I molecules on infected cancer cells, as this occurs in non-sterile tumors<sup>181</sup>. The immunotherapy of superficial bladder cancer by instillation of Bacille Calmette Guérin (BCG, an attenuated strain of *Mycobacterium tuberculosis*) is based on the infection of such cancer cells by BCG and their subsequent recognition by immune cells<sup>182</sup>. Of note, in patients that exhibit a preexisting immune response against BCG, this immunotherapy is particularly efficient<sup>183</sup>. Moreover, systemic immune responses against uropathogenic *Escherichia coli* (which infect uroepithelial carcinoma cells) correlate with therapeutic responses to PD-1 blockade in patients with muscle-invasive bladder cancer.<sup>174</sup>

A sizeable fraction of tumor infiltrating T cells recognizes viral antigens associated with low-pathogenic chronic infections such as Cytomegalovirus and Epstein Barr virus. Such T lymphocytes are found in the tumor infiltrate as ‘bystanders’<sup>184</sup> and may kill cancer cells in a non-specific fashion via the interaction between CD95 (on malignant cells) and CD95 ligand (on T cells)<sup>185</sup>. Thus, prior viral infection may determine the treatment response as shown for experimental lung cancer treated with IL15<sup>186</sup>. Active lung viral infection with seasonal influenza (Flu) virus favors immune infiltration of the TME and improves clinical outcome of mice and humans harboring lung tumors<sup>187,188</sup>. Conversely, acute Flu infection in melanoma bearing mice diverts antitumor effector CD8<sup>+</sup> T cells to the infected lung away from melanoma lesions and enhances tumor growth<sup>187</sup>. The clinical relevance of these findings was confirmed by analyzing a database comprising 30,000 lung cancer patients. Patients with  $\geq 1$  hospitalizations for influenza virus infection after cancer diagnosis exhibited decreased lung cancer-specific and overall mortality<sup>188</sup>.

In conclusion, both pre- and post-diagnostic infections affect cancer prognosis.

**Iatrogenic inhibition of immunotherapy.** A number of comedications interfere with the efficacy of ICIs, as discussed above for acetaminophen<sup>158</sup> and glucocorticoids<sup>86,87</sup>. For example, both in cancer patients and in preclinical models, the use of broad-spectrum antibiotics reduces the antitumor effects of ICIs<sup>189,190</sup> and anti-CD19 CAR T cells both in mice and human<sup>191</sup>. This is likely due to the



immunosuppressive dysbiosis associated with the diminution of beneficial bacteria from the *Bifidobacterium*, *Blautia* and *Ruminococcus* genera, as well as with the relative overrepresentation of harmful bacteria from the genus *Veillonella* or *Hungatella*<sup>190,191</sup>. Mouse experimentation indicates that the gut microbiota has a systemic adjuvant effect that is required for humoral vaccine responses<sup>192</sup> as well as for ICI effects<sup>189,193</sup>. Such effects likely rely on the avoidance of pro-inflammatory disruption of the intestinal barrier, effects on the gut-associated immune system, the avoidance of hypovitaminosis and spermidine depletion (because bacteria generate vitamins A, B3, B6, B12 and polyamines in the gut), the generation of microbiota-associated molecular patterns acting on pattern recognition receptors (such as lipopolysaccharide acting on TLR4 or cytosolic double-stranded DNA acting on the c-GAS/STING pathway) and the microbial production of short-chain fatty acids such as pentanoate and butyrate, which enhance the effector function of cytotoxic T lymphocytes<sup>190,194</sup>.

Efforts are underway to develop improved guidelines for the avoidance of iatrogenic immunosuppression, as well as to identify prebiotics (i.e., agents that expand useful bacteria), probiotics (i.e., specific microbial species with immunostimulatory properties) and postbiotics (i.e., the products and metabolites of such microbes) for the amelioration of cancer immunotherapies<sup>195</sup>.

## Concluding remarks and perspectives

The ever more profound understanding of communication networks that connect different organs and functions in our body is currently changing the scientific foundations of cancer research and clinical oncology. Indeed, processes occurring outside of the tumor including at the levels of systemic metabolism, inflammation and immunity, as well as neuroendocrine circuitries dictate the trajectory of malignant disease through molecularly defined biological mechanisms (**Fig. 2**). Moreover, underlying conditions including aging, comorbidities and comedications profoundly influence the prognosis and therapeutic response of cancer patients.

Aging has a major and decisive impact as a temporary variable that increases the probability of malignant disease and inexorably erodes the fitness of the cancer bearing host, thus reducing the therapeutic response<sup>196</sup>. Although aging is the strongest risk factor for cancer, it is modifiable in thus far that chronological aging (measured in years) and biological aging (measured with suitable fitness tests and molecular biomarkers or ‘clocks’) can occur on different scales. Clinical trials are now evaluating the possibility to halt, decelerate or reverse the development of age-associated diseases including cardiovascular events, neurodegeneration, lung fibrosis and sarcopenia<sup>197</sup>. It will be important to understand whether such antiaging medicines (or ‘geroprotectors’) might be used to accompany

anticancer treatments, for instance for the reduction of the side effects of chemotherapy as well as for the increase of anticancer immunosurveillance.

Prevalent comorbidities like obesity, diabetes, dyslipidemia, atherosclerosis, autoinflammatory and autoimmune disorders, dysbiosis, infections and psychiatric disease affect the general health of cancer patients and may directly influence tumor progression by excessive trophic signaling, elevated local inflammation as well as systemic immunosuppression. Moreover, such conditions give rise to pharmacological treatments that may be detrimental for the outcome of cancer immunotherapies, as this has been documented for antibiotics, acetaminophen and corticosteroids. Other comedications apparently have a positive effect on selected malignancies, as this has been shown for ASA, nonspecific  $\beta$ -blockers and lipophilic statins. Careful epidemiological studies might unravel additional negative and positive interactions between comedications and oncogenesis of tumor progression. Such studies might help to establish guidelines for the avoidance of negative pharmacological interactions. Moreover, they might inspire future experimentation to identify new oncological (co-)treatments. The question arises whether old and novel drugs should be systematically screened for cancer-modulatory activities in suitable animal models. Given the importance of immunosurveillance for the cancer-host equilibrium, it would be advisable to perform such screens in normal, immunocompetent mice bearing mouse tumors or in humanized mice bearing human cancers along with a histocompatible human immune system.

In light of the accumulating evidence in favor of a bodywide, ecological view of neoplasia, so-called ‘holistic’ approaches for cancer therapy including lifestyle interventions, nutritional and psychiatric counseling, as well as pharmacological treatments designed to mitigate or reverse conditions like obesity, dyslipidemia, depression, anxiety, chronic inflammation and dysbiosis, cannot be (dis)regarded anymore as mere quackery. Rather than postponing such ‘holistic’ interventions to palliative care, they should be part of the management of patients as soon as cancer diagnosis has been established. Guided by the knowledge that extratumoral processes are an integral part of malignant disease, diagnostic procedures and biomarker discovery should not focus exclusively on the tumor. Rather, they should evaluate bodywide derangements that contribute to tumor progression as well as the progressive deterioration of patient health. Similarly, biomedical research should give more room to the ecological exploration of malignant disease with its widespread impact on the host beyond malignant dissemination, as well as its multifactorial modulation by extratumoral host factors (**Box 1**).

Future investigation must determine the hierarchy and trajectory of systemic derangements affecting oncogenesis and tumor progression, pinpoint biomarkers that accurately spot individuals at risk of cancerization and faithfully reflect cancer-relevant bodywide alterations, and identify nodes in the interconnected pathogenic cascades that are particularly susceptible to cancer prevention, interception and treatment. It is our firm belief that, driven by molecular exploration and an ever-stronger

mechanistic rationale, whole-body interventions will constitute a welcome add-on to the existing oncological armamentarium (**Fig. 3**). In addition, future research must address wider aspects of the ecosystem including cultural, racial, and socio-economic factors that affect oncological practice.

**Author contributions:** GK wrote the first draft and then received major input from JM, MM, FA and LZ. All authors have read, edited and approved the paper.

**Data availability statement:** The paper does not contain any original or unpublished data.

**Acknowledgments:** GK and LZ are supported by the Ligue contre le Cancer (équipe labellisée); Agence National de la Recherche (ANR) – Projets blancs; Cancéropôle Ile-de-France; Fondation pour la Recherche Médicale (FRM); a donation by Elior; Equipex Onco-Pheno-Screen; Gustave Roussy Odyssey, the European Union Horizon 2020 Projects Oncobiome and Crimson; Institut National du Cancer (INCa); Institut Universitaire de France; LabEx Immuno-Oncology (ANR-18-IDEX-0001); a Cancer Research ASPIRE Award from the Mark Foundation; the RHU Immunolife; Seerave Foundation; SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); and SIRIC Cancer Research and Personalized Medicine (CARPEM). This study contributes to the IdEx Université de Paris ANR-18-IDEX-0001. JLM acknowledges the Transdisciplinary Research in Energetics and Cancer Research Training Workshop R25CA203650 and the MD Anderson Cancer Center (MDA) Center for Energy Balance in Cancer Prevention and Survivorship and is supported by ASCO/CCF, the Melanoma Research Alliance, the Elkins Foundation, Seerave Foundation, Rising Tide Foundation, the Mark Foundation for Cancer Research, MDA Melanoma SPORE Developmental Research Program Award, MDA Physician Scientist Program and MDA Moonshot Program. MM was supported by NIH grants U24 AI118644-05S1, R01CA257195 and R01CA254104 (Tumor macs), as well as by the Samuel Waxman Cancer Research Foundation. AF received ANR funding for IHU-B PRISM

**Conflicts of interest:** GK has been holding research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Tollys, and Vascage. GK has been consulting for Reithera. GK is on the Board of Directors of the Bristol Myers Squibb Foundation France. GK is a scientific co-founder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio. GK is the inventor of patents covering therapeutic targeting of aging, cancer, cystic fibrosis and metabolic disorders. GK's brother, Romano Kroemer, was an employee of Sanofi and now consults for Boehringer-Ingelheim. JM has served in advisory roles for BMS, Merck, and Roche. MM reports grants from Regeneron, Inc, outside the submitted work. FA has grants and advisory roles (compensated to the hospital) for Daiichi Sankyo, Pfizer, Novartis, Astra Zeneca, Lilly, Roche. LZ has held research contracts with 9 Meters Biopharma, Daiichi Sankyo, Pilege, was on the on the Board of Directors of Transgene, is a cofounder of everImmune, and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota.

### Box 1: Future questions for the ‘ecological’ exploration of cancer

- Can the **circulating metabolome** be related to cancer diagnosis, progression and prognosis? Are their diagnostic/prognostic biomarkers relevant to metabolism, and are there metabolites that impact cancer in a positive or negative fashion. What is the source of such metabolites (endogenous, nutritional, bacterial...)? How can nutritional, microbial or pharmacological interventions on metabolism be used for improving therapeutic responses?
- Which **neuroendocrine factors** do impact the development of cancers in a positive or negative fashion? What is their source? On which cell types do they act within the tumor? Can they be harnessed for improving therapeutic responses? Do aging- or obesity-associated neuroendocrine factors affect cancers in a negative fashion? And can they be normalized for therapeutic purposes?
- How can **inflammation or fibrosis** be avoided in the context of oncogenesis and tumor progression? What underlying conditions (hypercaloric regimen, carbotoxicity, lipotoxicity, sedentarity...) can be targeted to avoid inflammation and fibrosis? Which are the best strategies to pharmacologically suppress age-associated inflammation and fibrosis without compromising immune function? And would such strategies mediate tangible anticancer effects or improve the efficacy of standard of care?
- How is the **trafficking of anticancer effectors** (e.g., dendritic cells, NK cells and T lymphocytes) **and immunosuppressive cells** (e.g., regulatory T cells and myeloid-derived suppressor cells) into the tumor regulated? Can this trafficking be influenced by manipulations of chemokine gradients or homing mechanisms to ameliorate the tumor microenvironment? What is the impact of **past and ongoing viral infections** on cancer immunosurveillance? Are their cellular or humoral **immunological cross-reactivities** between cancer-associated antigens and autoimmunity-related or bacterial antigens? Can they be harnessed to stimulate local immunosurveillance?
- Which **comedications** acting on frequent age- or cancer-associated comorbidities (e.g., cardiovascular and neuropsychiatric disorders) or unrelated comorbidities (e.g., allergic and autoimmune disorders) impact the natural progression and therapeutic responses of cancers? Can we design systematic screens to identify FDA-approved drugs that affect specific pro-carcinogenic or tumor-suppressive (including immunostimulatory) pathways? What are the mechanisms of negative and (more interestingly) positive effects of such comedications on treatment outcome?

**Table 1:** Examples of clinical Phase 2 or Phase 3 trials exploring ‘ecological’ interventions on cancer

Intervention	Clinical or preclinical rationale	Examples of ongoing clinical trials
<b>General metabolism</b>		
Reduced caloric intake/fasting	Enhanced T cell infiltration and local interferon- $\gamma$ production in breast cancer patients <sup>198</sup>	NCT04248998: Fasting mimicking diet with or without metformin in TNBC NCT05503108: Fasting mimicking diet to improve chemotherapy in hormone receptor-positive BC
Ketogenic diet	Improved overall survival in women with locally advanced breast cancer <sup>199</sup> .	NCT05119010: Ketogenic diet concomitant to nivolumab and ipilimumab for metastatic RCC
High fiber diet	High fiber diet is associated with improved responses to melanoma immunotherapy <sup>200</sup> .	NCT04645680: Whole foods diets in melanoma patients undergoing immunotherapy NCT04866810 : High fiber diet + exercise in Nivolumab/Relatlimab treated melanoma
<b>Specific metabolites</b>		
3-hydroxybutyrate	Oral supplementation stimulates immunotherapy outcome in mice <sup>39</sup> .	NCT05119010: Oral supplementation concomitant to nivolumab and ipilimumab for metastatic renal cell carcinoma
Short chain fatty acids (SCFA)	Oral supplementation decreases liver metastasis and improves host immune response against CT26 colon cancers <sup>201</sup> .	NCT04700527: Effects of SCFA (butyrate and propionate) supplementation in subjects receiving abdominopelvic radiotherapy
Nicotinamide	Oral supplementation reduces non-melanoma skin cancers in susceptible individuals <sup>35</sup> .	NCT02416739: Effects against NSCLC NCT03769285: Skin cancer prevention in transplant recipients
Vitamin D3	Reduces risk of ductal carcinoma in situ of the breast <sup>38</sup> . Reverses the exhausted phenotype of cytotoxic T cells in cancer patients <sup>202</sup> .	NCT04094688: Advanced or metastatic CRC treated with chemotherapy and bevacizumab NCT04677816: Neoadjuvant BC chemotherapy
<b>Statins</b>		
Atorvastatin	Use of lipophilic statins (such as atorvastatin, lovastatin, rosuvastatin and simvastatin) is associated with a diminished risk of lethal prostate cancer <sup>44</sup> as well as that of HCC, irrespective of its etiology (alcohol abuse, non-alcoholic steatohepatitis or viral infection,) <sup>45</sup> . In breast cancer patients, post-diagnostic statin use is associated with improved recurrence free, overall and cancer-specific survival <sup>46</sup> .	NCT03024684: Preventing HCC recurrence after curative treatment NCT03872388: Stage IIb-III TNBC without pathological complete response after neoadjuvant chemotherapy NCT04026230: Prostate cancer under androgen depletion therapy NCT04379999: Combination with aspirin in Lynch syndrome NCT04601116: Estrogen receptor-positive BC treated with standard of care NCT04767984: Reducing colon cancer risk in ulcerative colitis
Simvastatin	In patients with RCC or NSCLC, statin administration is associated with improved therapeutic responses to PD-1 blockade <sup>47,48</sup> .	NCT02968810: Preventing HCC in cirrhosis NCT03324425: Dual anti-HER2 therapy of metastatic BC NCT04457089: Reducing progression of platinum sensitive ovarian cancer NCT05464810: Hormone receptor-positive BC treated with letrozole
<b>Neuro-endocrine factors</b>		

Beta-blockers (propranolol)	Post-diagnostic use of beta blockers reduces cancer-specific mortality in a retrospective meta-analysis (HR = 0.89; CI: 0.79-0.99) <sup>91</sup> . Randomized trials indicate that perioperative beta blockade improves biomarkers of metastasis in BC or CRC <sup>101,102,203</sup> .	NCT05451043: Boosting immunotherapy with durvalumab or tremelimumab in HCC, cholangiocarcinoma and PDAC NCT03384836: Combination with pembrolizumab in stage IIC-IV melanoma NCT04682158: Combination with standard chemoradiation for esophageal adenocarcinoma
Glucocorticoid receptor antagonist (mifepristone)	In cancer patients treated with immune checkpoint inhibitors, corticosteroid use is an unfavorable prognostic factor <sup>86,87</sup> . Mifepristone reestablishes immunosurveillance in stressed mice <sup>88</sup> .	NCT03225547: HER2-negative BC treated with pembrolizumab NCT02788981: TNBC treated with nab-paclitaxel NCT03583710: Adrenocortical cancer treated with chemotherapy alone or together with the glucocorticoid synthesis inhibitor mitotane
IGF1R blockade	Pharmacological blockade of IGF1R with picropodophyllin or linsitinib improves anticancer immunosurveillance <sup>84</sup> .	NCT02145741: Xentuzumab (anti-IGF1R antibody) against solid tumors NCT03099174: Xentuzumab plus abemaciclib in BC and NSCLC NCT05110495: Xentuzumab before radical prostatectomy
<b>Anti-inflammatory drugs</b>		
Acetylsalicylic acid (ASA) and other non-steroidal anti-inflammatory drugs such as celecoxib and niclosamide	ASA has broad chemopreventive effects, in particular against gastrointestinal cancers) <sup>147,148</sup> and HCC <sup>149</sup> . ASA reduces cancer-specific death in patients with BC and CRC <sup>150,151</sup> . NSAIDs other than ASA also reduce the frequency of proximal colon cancers and improve their prognosis <sup>153</sup> . Randomized controlled trials confirmed the capacity of celecoxib to reduce polyp incidence in patients with familial adenomatous polyposis, as well as in patients that already undergone the resection of a sporadic adenomatous polyp <sup>153-155</sup> ;	NCT02521285: Avoidance or recurrence of Barrett esophagus after radiofrequency ablation (ASA) NCT02467582: Colon cancer with PIK3CA mutation treated with adjuvant chemotherapy (ASA) NCT02804815: Avoidance of recurrence of non-metastatic solid tumors treated with standard of care (ASA) NCT02885974: Localized, muscle-invasive bladder cancer treated with chemotherapy (celecoxib) NCT02927249: Prevention of recurrence of HER2-negative stage II-III BC post-therapy (ASA) NCT02945033: Colon cancer with PIK3CA mutation treated with adjuvant ASA NCT02965703: Avoidance of progression of colon adenoma (ASA) NCT03290820: Nasopharyngeal carcinoma under chemoradiotherapy (ASA) NCT03326791: Liver metastasis of CRC, post-metastasectomy (ASA) NCT03396952: Melanoma treated with ipilimumab + pembrolizumab (ASA) NCT03464305: Survival of stage II and III colon cancer patients post-treatment (ASA) NCT03819101: Castration-resistant PC under standard of care plus ASA and/or atorvastatin NCT03480776: Prevention of ovarian cancer in women with BRCA1/2 mutations (ASA) NCT03899987: Neoadjuvant treatment of prostate cancer with rintatolimod and interferon- $\alpha$ 2b (ASA) NCT04188119: Neoadjuvant treatment of TNBC cancer together with avelumab (ASA) NCT04214990: Prevention of gastric cancer after endoscopic resection of early lesions (ASA) NCT04296851: Chemoprevention in familial adenomatous polyposis (niclosamide)

		<p>NCT04379999: Prevent of Lynch syndrome cancer together with atorvastatin (ASA)</p> <p>NCT02497820: Prevention of Lynch syndrome cancers (ASA)</p> <p>NCT05056896: Prevention of CRC (ASA)</p> <p>NCT05080946: Ovarian cancers treated with neoadjuvant chemotherapy (ASA)</p> <p>NCT05411718: Prevention of Lynch syndrome cancers (ASA versus naproxen)</p> <p>NCT05402124: Prevention of colon cancer after resection of adenoma(s) during colonoscopy</p> <p>NCT05462613: Metastatic colon cancer treated with regorafenib and metronomic chemotherapy</p>
IL1 $\beta$ blocking antibody (canakinumab)	Reduced incidence of NSCLC in patients with atherosclerosis in a Phase 3 trial, coupled to a reduction in C-reactive protein (CRP) and IL6 levels, which are risk factors for lung cancer development <sup>163,164</sup> .	<p>NCT04905316: HCC with chemotherapy, radiotherapy and durvalumab</p> <p>NCT03447769: Adjuvant therapy of NSCLC</p> <p>NCT03968419: Neoadjuvant therapy of NSCLC, alone or in combination with pembrolizumab</p> <p>NCT03631199: Squamous NSCLC treated with platinum chemotherapy plus pembrolizumab</p> <p>NCT04789681: Prevention of NSCLC in patients with high-risk pulmonary nodules</p> <p>NCT04581343: Metastatic prostate cancer treated with spartalizumab, nab-paclitaxel + gemcitabine</p> <p>NCT04028245: Localized clear cell renal cancer treated with spartalizumab</p> <p>NCT03484923: Previously treated unresectable or metastatic melanoma treated with spartalizumab</p>
IL6 blockade (tocilizumab)	Improved outcome of CTLA-4 blockade against mouse melanoma with more local T cell infiltrate and less MDSC and macrophages <sup>136</sup> .	<p>NCT02767557: PDAC treated with nab-paclitaxel and gemcitabine</p> <p>NCT03193190: PDAC treated with chemotherapy and atezolizumab</p> <p>NCT03708224: Head &amp; neck squamous cancer with neoadjuvant atezolizumab</p> <p>NCT03821246: Prostate cancer with neoadjuvant atezolizumab</p> <p>NCT03869190: Urothelial carcinoma with atezolizumab</p> <p>NCT03999749: Melanoma with ipilimumab and nivolumab</p> <p>NCT04338685: Primary HCC or cancers with liver metastases treated with a TLR7 agonist</p> <p>NCT04496674: Lung squamous carcinoma with bispecific PSMaXCD3 antibody</p> <p>NCT04524871: Advanced HCC treated with atezolizumab + bevacizumab</p> <p>CT04551352: TYRP1-positive melanoma treated with anti-TYRP1/CD3 T-cell engager</p> <p>NCT04691817: Melanoma in combination with atezolizumab after initial immunotherapy failure</p> <p>NCT04940299: Melanoma, lung and urothelial carcinomas treated with ipilimumab + nivolumab</p> <p>NCT05129280: MAGE-A4-positive melanoma with anti-MAGE-A4 TCR/anti-CD3 bispecific</p>
Senolysis (removal of senescent cells)	Removal of senescent cells reduces the side effects of doxorubicin-based chemotherapy while improving its	NCT03889795: Advanced solid cancers, treated with metformin, digoxin (senolytic) + simvastatin

	efficacy and the probability of relapse <sup>141</sup> . Patients treated with digoxin show improved overall survival with breast, colorectal, head & neck, and liver cancer, as well as reduced risk of prostate cancer <sup>145,146</sup> .	NCT04141995: PDAC with adjuvant FOLFIRIOX chemotherapy (digoxin) NCT04733534: Accelerated aging and frailty in adult survivors of childhood cancer treated with senolytics (dasatinib + quercetin)
<b>Systemic immunity</b>		
Mycobacterium tuberculosis (Mtb) and Bacille Calmette Guérin (BCG)	Preexisting BCG-specific T cells improve intravesical immunotherapy for bladder cancer <sup>183</sup> .	NCT03091660: BCG therapy of high-grade non-muscle invasive bladder cancer after intradermal immunization with BCG NCT03191578: BCG therapy of superficial bladder cancer after immunization against Mtb
FLT3 ligand	Systemic injections of Flt3L favor the expansion of dendritic cells of the cDC1 subset in mice, improving the outcome of immunotherapy <sup>204</sup> . Flt3L levels are increased by oxaliplatin in patients with high-risk rectal cancer, associated with longer progression-free survival <sup>205</sup> .	NCT02839265: Advanced NSCLC under radiotherapy NCT04491084: NSCLC with CD40 agonist antibody and radiotherapy NCT04616248: Metastatic BC with radio-immunotherapy NCT05029999: Metastatic TNBC with CD40 agonist and chemotherapy
Influenza vaccine	Patients hospitalized for influenza virus infection after NSCLC diagnosis exhibit decreased overall mortality <sup>188</sup> .	NCT04591379: Neoadjuvant intratumoral flu vaccine in early CRC NCT04697576: Melanoma patients receive intramuscular and intralesional flu vaccine

NB: The table does not list systemic immunotherapies targeting checkpoints, cytokines interferons, interleukins and pattern recognition receptors. Moreover, pure lifestyle interventions (such as exercise, meditation or yoga) have not been listed. Only frequent solid tumors have been included.

Abbreviations: BC, breast cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer; PC, prostate cancer; PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell carcinoma; TNBC, triple negative breast cancer;



## Legends to Figures

**Fig. 1:** Paradigm shifts in cancer research and therapy. The progressive complexification of the realm of oncology is shown in steps from left to right. A purely cancer cell-centric view of the tumor (A) has given way to an ever more complex view of cancer with the inclusion of stromal elements (B) and myeloid and lymphoid cells participating in immunosurveillance (C). More recently, the influence of extratumoral effects on cancer biology has been realized (D).

**Fig. 2:** Molecules and pathways linking the different components of the bodywide ecosystem to the tumor microenvironment (TME). Systemic metabolism (A), neuroendocrine factors (B), chronic inflammation (C) and systemic immunity (D) mediate long-distance effects on TME via blood flow, lymph and nerves that connect the cancer to the rest of the body.

Abbreviations: 5-HT, 5-hydroxytryptamine; CHIP, clonal hematopoiesis of undetermined prognosis; GABA, gamma-aminobutyric acid; IGF1, insulin growth factor-1; IL, interleukin; NPY, neuropeptide Y; SASP, senescence-associated secretory phenotype

This figure was generated with the help of Biorender.

**Fig. 3:** Future management of cancer patients using combinations of systemic and tumor-targeted interventions, as well as the avoidance of noxious comedications. Currently used tumor-targeted therapies and immunotherapies (which are often combined among each other) will be complemented in the future by ecological interventions on extratumoral derangements. Altogether, these treatments affect the bodywide ecosystem that includes the tumor.

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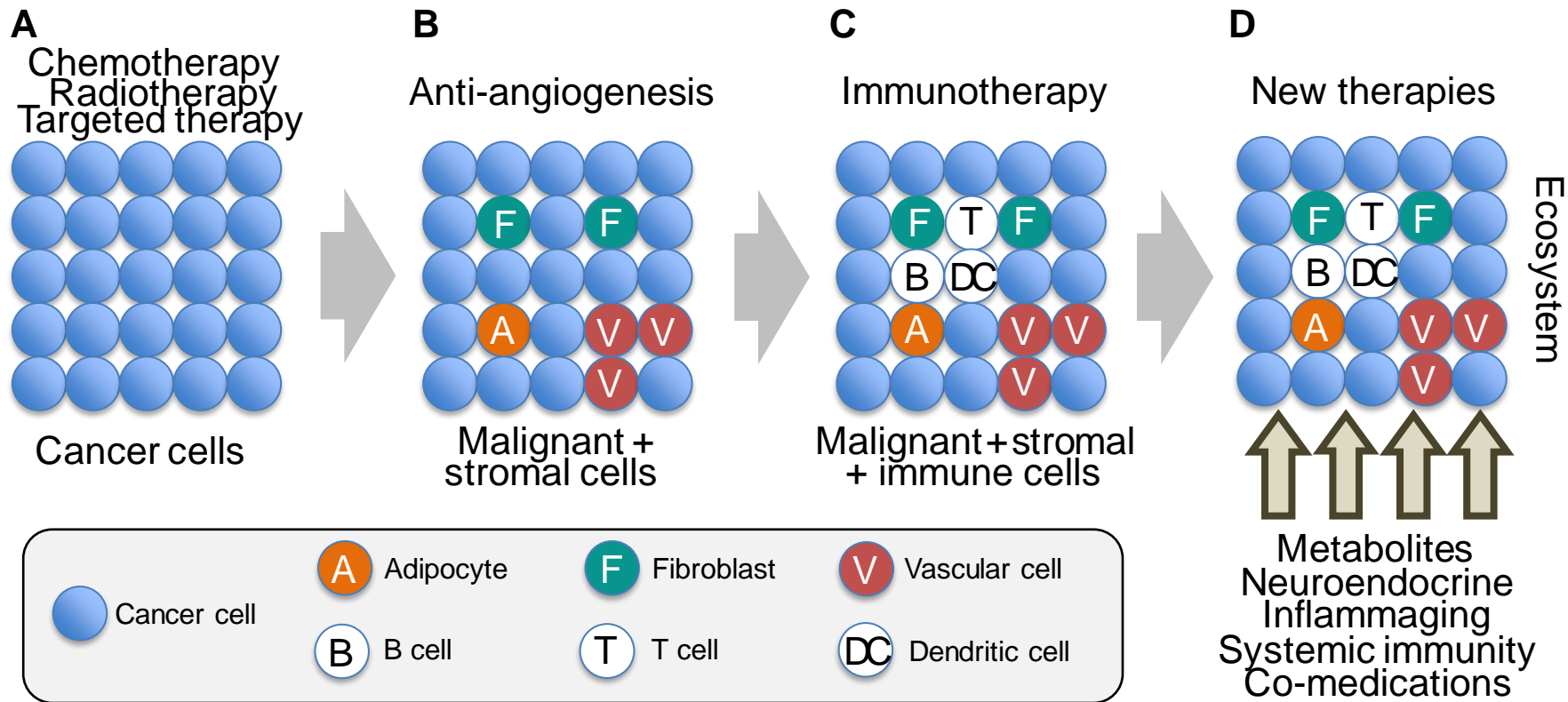
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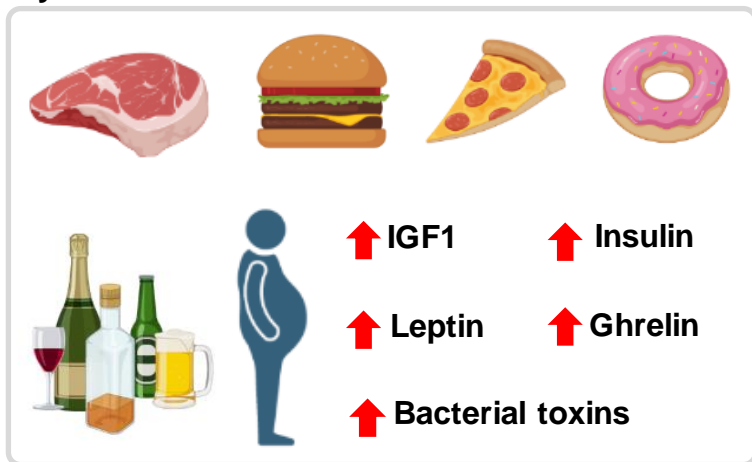
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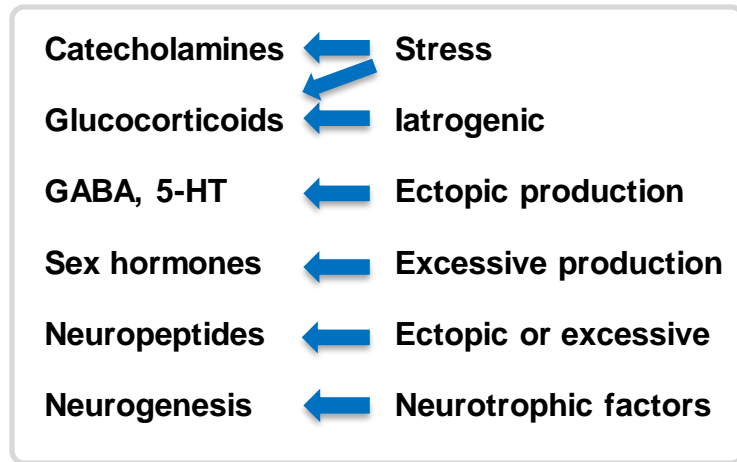


**Fig. 1**

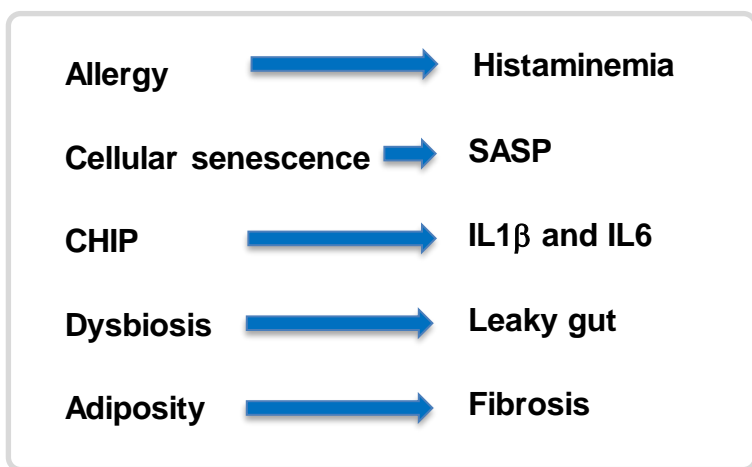
## Systemic metabolism

**A**

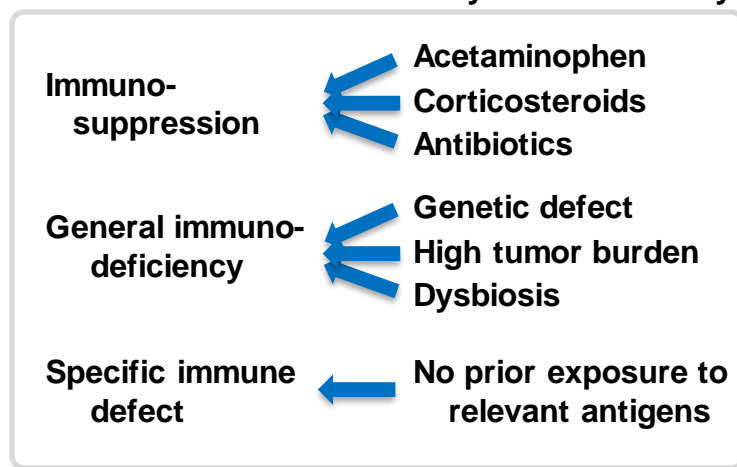
## Neuroendocrine factors

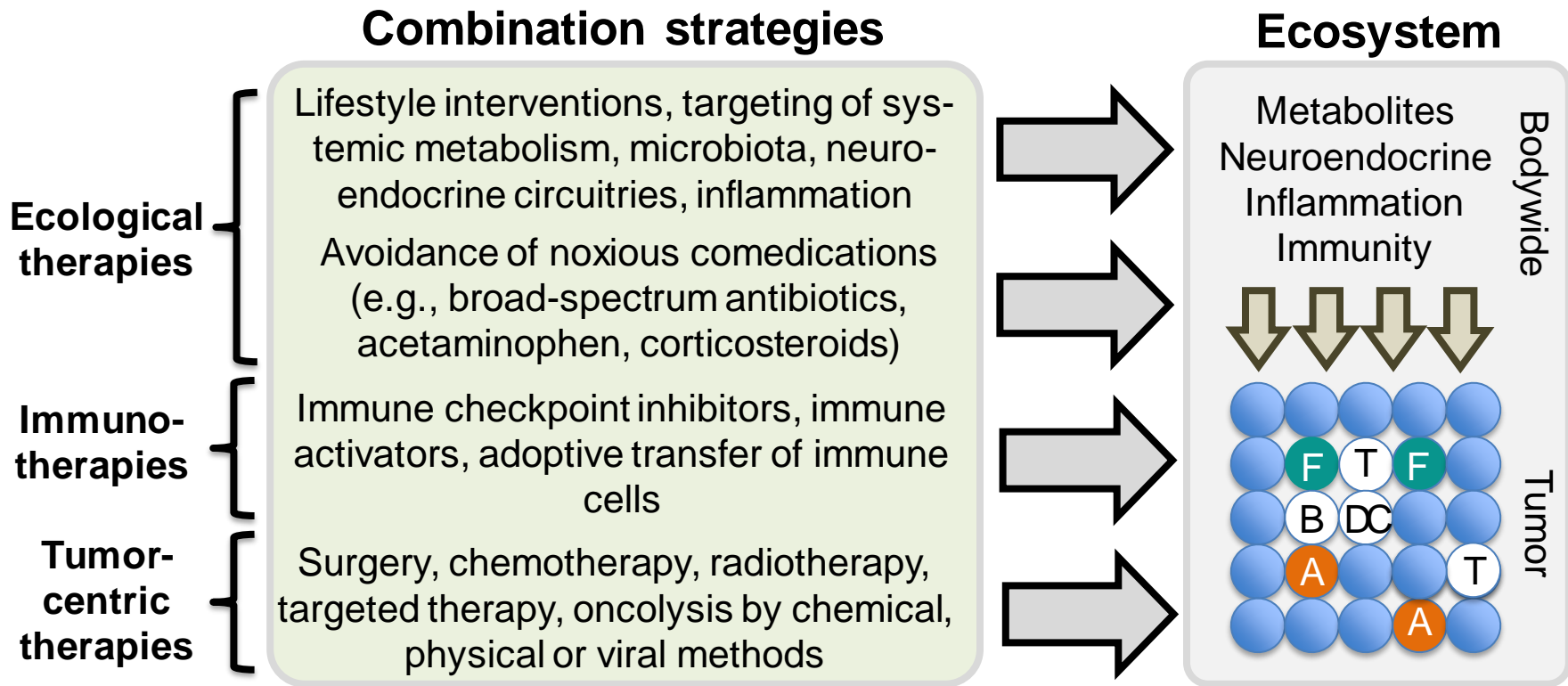
**B**

## Chronic inflammation

**C**

## Systemic immunity

**D****Fig. 2**



**Fig. 3**