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REVIEW

Poor prognosis outcome tumors, bacteria-infected tumors and nanodrugs: current evidence and hypotheses towards a paradigm change for treatment

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ABSTRACT New therapies and supportive care have converted several cancer types into chronic conditions. Yet, some tumors exhibit features reproducibly correlated with poor prognosis outcome (PPO-tumors). Bacteria in a tumor environment can inactivate chemotherapeutics and are a feature of PPO-tumors, although standard diagnostic tests for tumor infections do not exist. Optimism is high for nanotechnologic innovations but nanoparticulate chemotherapeutics based on enhanced permeability and retention in a human tumor environment have only shown limited treatment benefits. Moreover, treatment of infected tumors in animals with stimuli-responsive nanocarriers loaded with an antibiotic/chemotherapeutic combination has demonstrated limited benefits compared to treatment with combinations of carrier-free antibiotics and chemotherapeutics. Development of nanoparticulate chemotherapeutics with significant benefits in human clinical use is estimated to take several decades, which is too long for patients with PPO-tumors. Herein we hypothesize the following: 1-all diagnosed PPO-tumors are infected with bacteria; 2-all PPO-tumors in mice and humans exhibit enhanced permeability to chemotherapeutics; and 3-all diagnosed PPO-tumors must be treated from the onset with a combination of carrier-free antibiotics and chemotherapeutics. Each hypothesis was critically evaluated and judged plausible and clinically acceptable. Potential clinical treatment of PPO-tumors, presuming bacterial infection without diagnosis, with an approved antibiotic and chemotherapeutic free drug combination requires a paradigm change in treatment concept towards more lenient antibiotic use. However, many cancer patients already require antibiotics during chemotherapeutic treatment and combined carrier-free antibiotic/chemotherapeutic treatment may provide an immediate pathway to re-sensitize PPO-tumors to clinically used chemotherapeutics and alter the prognosis to a more favourable outcome.

KEYWORDS Bacteria-infected tumors; nanodrug combinations; paradigm change; hypotheses

Introduction

Solid tumors are embedded in a highly complex and dynamic tumor microenvironment (TME) composed of malignant cells, stromal components, immune infiltrates, vasculature, extracellular matrix, and diverse physicochemical gradients[1,2]. This microenvironment is spatially and temporally heterogeneous, profoundly influencing tumor progression, therapeutic response, and drug transport[3,4]. Advances in targeted therapies, immunotherapies, better diagnostics, and supportive care have allowed many cancers to become managed as chronic conditions[5-7]. Hormone therapies have turned metastatic breast and prostate cancer, once rapidly progressive, into diseases that can often be held in control for years. Chemotherapy has laid the foundation for long-term remission of hematologic cancers. Targeted therapies using small molecules or therapeutic monoclonal antibodies hitting specific molecular targets essential for tumor survival or growth have transformed chronic myeloid leukemia and several breast and ovarian cancers into chronic conditions. Melanoma and lung cancer patients have particularly benefited from immunotherapies. Whether or not a tumor can be managed chronically

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depends heavily on the stage at diagnosis, molecular subtype, and patient health status. However, "chronic" does not mean "cured," and addressing cancer as a chronic condition requires continuous supportive care, including diagnostic monitoring and treatment with low-dose chemotherapeutics. Current clinical treatments add 5–20+ years to lives of patients with select early-stage cancers[8,9]. For some cancers the lifetime extension remains limited to months and a maximum range of 3–5 years.

For these tumors, our current understanding of the evolving TME may be insufficient to drive meaningful advances in treatment efficacy and drug delivery. In this context, bacterial presence has been increasingly observed within the TME. Bacteria enter the TME by breaching mucosal barriers, such as in the esophagus, lungs, colon, or cervix, by invasion of adjacent tissue or by hematogenic invasion amongst others from the oral cavity or the intestines[10]. Once present, these bacteria may become integral components of the TME and influence tumor initiation, progression, and therapeutic response through multiple mechanisms (**Figure 1**).

Scope and limitations of this review

This review synthesizes current evidence from the oncologic, microbiologic, and nanomedicinal literature to determine whether bacteria within tumors represents an overlooked contributor to persistently poor prognosis outcomes in a subset of cancers. Despite major advances in targeted therapies and immunotherapies, some tumors remain predictably poorly responsive to current treatment strategies. Rather than focusing on a single cancer entity, this review considers common clinical and biological features shared by such predictably poor prognosis outcome tumors (PPO-tumors) across different cancer types to evaluate whether bacterial involvement could plausibly contribute to the behaviour.

The scope of this review is therefore not to establish universal causality between intratumoral bacteria and tumor aggressiveness or therapy resistance nor to claim that all predictably PPO-tumors are driven by bacterial infection. The associations discussed are interpreted as correlations that may reflect causative, contributory, or consequential relationships, depending on the tumor context. A central limitation addressed throughout the review is the absence of clinically reliable methods to diagnose intratumoral bacterial infection *in vivo*, which restricts definitive attribution of bacterial involvement and necessitates cautious interpretation of post-resection and retrospective data.

Accordingly, this review emphasizes the consistency of observations, biological plausibility, and compatibility with known limitations of drug delivery and the TME over definitive proof. By explicitly defining these limitations, this review aims to provide a coherent and evidence-informed framework for re-examining treatment strategies for predictably PPO-tumors, while acknowledging current methodologic and clinical uncertainties inherent to this field.

Molecular and nanoparticulate chemotherapeutic transport mechanisms and delivery efficiencies in tumors

Currently, approximately 0.1% of systemically injected molecular chemotherapeutics free in solution are delivered to a tumor site[11]. For cancers still showing limited lifetime extension, it is expected that nanoparticulate chemotherapeutics with increased delivery efficiencies will prove to be beneficial for increasing the gain in a patient's longevity after diagnosis. Nanoparticulate chemotherapeutics can be divided in two groups[12]. Non-responsive nanocarriers show little or no interaction with the environment, while stimuli-responsive nanoparticles can selectively change properties to interact with tumor cells or blood vessel walls in the close vicinity of a tumor site. Systemically delivered nanoparticulate chemotherapeutics in rodents published between 2005 and 2015 were delivered into a solid tumor at median and mean efficiencies of 0.70% and 1.48%, respectively[13], which were higher than currently achieved efficiencies using molecular chemotherapeutics free in solution. It should be recognized that delivery efficiencies reported for molecular and nanoparticulate chemotherapeutics are not fixed or absolute quantities. These values depend strongly on experimental and clinical context, including the timing of measurement after administration, tumor growth or regression kinetics, vascular dynamics, and the analytical methods used to quantify drug accumulation. Consequently, such percentages should be interpreted as indicative rather than definitive metrics. While useful for broad comparative purposes, numerical delivery efficiencies alone should not be overemphasized when evaluating therapeutic effectiveness, translational relevance, or underlying biological mechanisms. Within this limitation, further refinement of the above data demonstrate that delivery efficiencies of nanoparticulate chemotherapeutics with diameters less than 100 nm and zeta potentials hovering around 0 mV, were found to be higher than 5%[13]. These non-responsive nanoparticles possessed little interaction with tumor cells or blood vessel endothelium. Results comprising 250 data points demonstrated that the delivery efficiencies of non-responsive nanoparticulate chemotherapeutics in rodents increase linearly with the square-root of the blood circulation half-lives up to 2.5 $h^{1/2}$ (**Figure 2A**), indicating a strong initial influence of diffusional mass transport. For longer circulation half-lives, delivery efficiencies decrease to below the anticipated level for diffusion-controlled mass transport, likely due to slow clearance from the blood circulation.

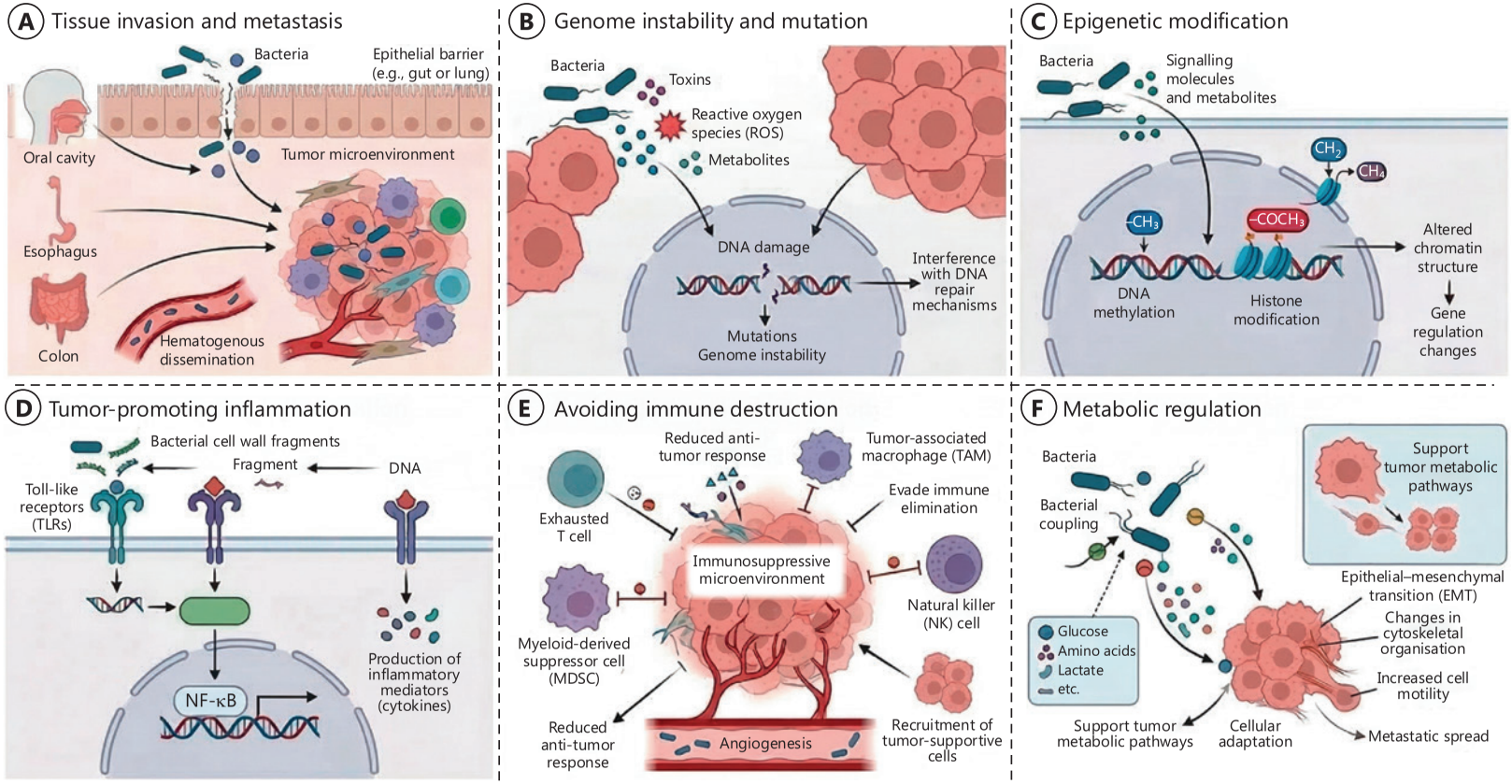


Figure 1 The role of intratumoral microbiota in the development of cancer[10]. (A) Tissue invasion and metastasis. Bacteria may enter the tumor microenvironment by breaching mucosal barriers (e.g., in the esophagus, lungs, colon, and cervix), by invasion of adjacent tissues, or through hematogenous dissemination (e.g., from the oral cavity or intestinal tract). Once present within tumors, microbial communities may interact with tumor cells, stromal elements, and immune cells through several mechanisms that may influence tumor initiation, growth, and treatment response. (B) Genome instability and mutation. Intratumoral bacteria may contribute to genomic instability through the production of toxins, reactive oxygen species, and other metabolites capable of inducing DNA damage. These processes can promote mutations, interfere with DNA repair mechanisms, and contribute to tumor heterogeneity. (C) Epigenetic modification. Microbial metabolites and signalling molecules may influence gene regulation through epigenetic mechanisms, such as DNA methylation, histone modification, and changes in chromatin structure, thereby altering tumor cell behaviour without modifying the underlying DNA sequence. (D) Tumor-promoting inflammation. Microbial components may activate innate immune receptors, such as Toll-like receptors, triggering signalling pathways, including NF-κB, and stimulating the production of inflammatory mediators. (E) Avoiding immune destruction. Chronic inflammation may promote tumor growth, angiogenesis, and the recruitment of tumor-supportive immune cell populations. Interactions between intratumoral bacteria and immune cells may contribute to the development of an immunosuppressive microenvironment. Modulation of T cells, natural killer cells, macrophages, and dendritic cells may reduce effective anti-tumor immune responses and allow tumor cells to evade immune-mediated elimination. (F) Metabolic regulation. Bacterial metabolism may alter the availability of nutrients and metabolites within the tumor microenvironment, influencing tumor cell metabolic pathways and supporting cellular adaptation to the metabolic constraints of the tumor niche. Microbial signalling may affect cell adhesion, epithelial–mesenchymal transition, and cytoskeletal organisation, potentially enhancing tumor cell motility and invasiveness and facilitating metastatic spread. Together, these processes illustrate how intratumoral microbiota may influence multiple aspects of tumor biology and may contribute to the complex microenvironment observed in certain cancers. The figures were created with BioRender.

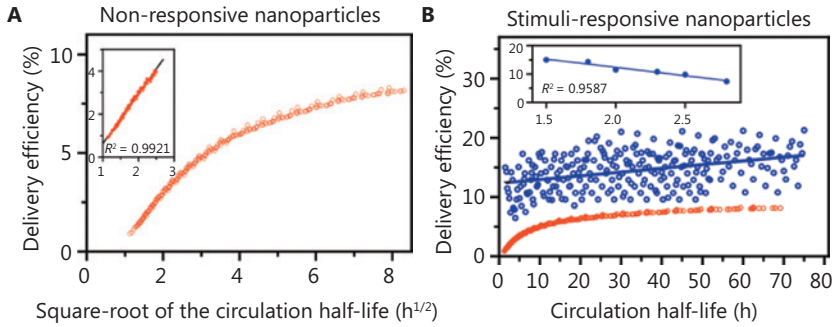


Figure 2 Tumor delivery efficiency for 250 published nanoparticulate chemotherapeutics as a function of circulation half-life in rodent models. (A) Delivery efficiency of non-responsive nanoparticles as a function of the square-root of the blood circulation half-life, together with the linear correlation coefficient, R^2, calculated for the data points up to 2.5 $h^{1/2}$. Data are taken from foundational references[11,13-15] published between 2010 and 2016. High-impact published reviews were taken as foundational references from which primary references were taken for these nanoparticle circulation data until 250 data points were obtained by AI-Deepseek/ChatGPT. Foundational references were verified by the authors. (B) A comparison of the delivery efficiency of non- and stimuli-responsive nanoparticles as a function of blood circulation half-lives. The initial decreasing trend in the data was calculated for data points up till 3 h, while remaining data reflect a slowly increasing trend. Data are taken from foundational references[16-22] published between 2020 and 2024, as described above for data for non-responsive nanoparticles.

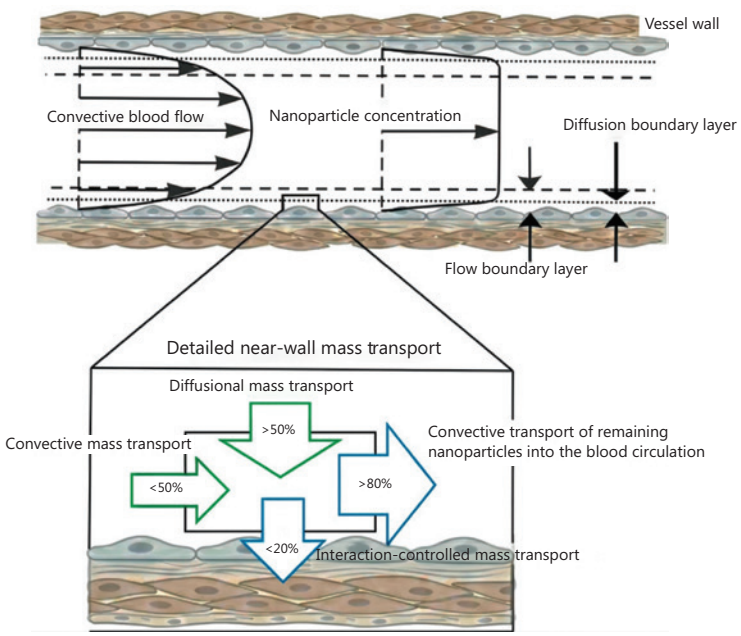


Figure 3 The interplay between different mass transport mechanisms[23] prevailing in a blood vessel near a tumor site. Convective blood flow is in the longitudinal direction of the vessel and follows a parabolic velocity curve over the vessel diameter with velocity decreasing to the vessel walls (flow boundary layer). Inside the flow boundary layer, diffusion starts to contribute to mass transport towards the vessel wall till the diffusion boundary layer, where in case of a suitable physico-chemistry of the nanoparticle surface, attractive interaction starts to contribute to mass transport. The enlarged box represents a near-wall volume unit with different nanoparticle in- (green arrows) and out-flow (blue arrows) mechanisms indicated. The widths of the respective arrows denote the relative contributions, as derived from Sherwood analysis of blood flow (Eq. 2) and the delivery efficiencies of stimuli-responsive nanoparticles in the blood flow.

Diffusion is not the only mass transport mechanism operating in a blood vessel in which convection- and interaction-controlled mass transport also has an important role (**Figure 3**). The importance of convective *versus* diffusional mass transport can be further elaborated upon by calculation of the Sherwood mass transport number[24], denoting the ratio

of convective over diffusional mass transport in absence of interaction (i.e., "perfect sink conditions") as follows:

$$\mathrm{Sh} = \frac{k\,L}{D} \quad (1)$$

where k is the mass transfer coefficient (m/s), L is a characteristic length (m), and D is the nanoparticle diffusion coefficient (m^2/s). Under conditions of confinement (e.g., a nanoparticle with a diameter, d_p, within a tube with diameter, D_t), a widely used form is:

$$\mathrm{Sh} = (2 + 0.6\,\mathrm{Re}_p^{1/2}\,\mathrm{Sc}^{1/3})\left(1 - \frac{d_p}{D_t}\right)^{-1.6} \quad (2)$$

where Re is the Reynolds number (defined as $[v\,L]/\nu$, in which v is the characteristic speed and ν is the kinematic viscosity) and Sc the Schmidt number (defined as $[\nu/D]$). For pure diffusion, Sherwood numbers are approximately 1, while Sherwood numbers $\gg$100 indicate pure convective mass transport. Sherwood numbers estimated for nanoparticles with a diameter of 100 nm under typical blood flow conditions range between 2 and 30, confirming diffusion-controlled mass transport with a significant contribution of convective blood flow.

More recent pH-responsive and other stimuli-responsive nanocarriers are negatively charged at physiologic pH (near 7.4) and highly hydrophilic[25]. These two properties enable stimuli-responsive nanocarriers to circulate for a long time in blood without loss or degradation of active components, reducing blood coagulation or complement and/or platelet activation. In the more acidic and hypoxic TME, pH-responsive nanocarriers can become positively charged and, depending on nanocarrier design, may disassemble to release the cargo. This charge reversal to positive values (>10 mV) prompts strong electrostatic double-layer attraction to tissue and enhanced retention, which contributes to increased delivery efficiency in the TME to median and mean efficiencies of 0.76% and 2.23%, respectively, as evaluated between 2005 and 2018[16]. These stimuli-responsive nanoparticles demonstrated a distinctly different influence of blood circulation half-lives on delivery efficiency than non-responsive counterparts (**Figure 2B**). Whereas non-responsive nanoparticulate chemotherapeutics display a narrow, well-defined relationship with minimal dispersion, stimuli-responsive nanoparticles span a much broader range of dispersion, consistent with diverse response mechanisms. The delivery efficiencies were initially high (10%–15%) at low blood circulation half-lives, exhibiting decreasing delivery efficiency with blood circulation half-lives up to 3 h due to fast, interaction-controlled blood depletion (**Figure 3**). However, once blood circulation half-lives exceed 3 h, convective-diffusional mass transport dominates over interaction. As a result, delivery efficiencies slowly increase by combination of convective, diffusional, and interaction-controlled mass transport to approximately 20% for blood circulation half-lives >20–25 h for select stimuli-responsive nanoparticulate chemotherapeutics (**Figure 2B**). Within the broad range of dispersion, other responsive nanoparticulate chemotherapeutics perform marginally better than non-responsive types. This finding indicated that for stimuli-responsive nanoparticles, responsiveness can constitute a strong driver for bypassing *in vivo* barriers limiting delivery of non-responsive nanoparticulate chemotherapeutics.

Yet, within the limitations of broadly distributing delivery efficiencies among different responsive nanoparticulate chemotherapeutics in rodent models, ≥80% of the administered nanoparticle doses still go off-target, which not only impacts clinical treatment efficacy but also elicits adverse drug events[26]. Extrapolating to human clinical situations, this finding implies administration of unreasonably high drug doses, making it imperative to overcome the challenges of how to further increase the delivery efficiencies of nanoparticulate chemotherapeutics, while encountering still substantial barriers reducing delivery[27]. This further development and clinical validation of nanoparticulate chemotherapeutics with truly improved delivery efficiency may require several decades of further research[13].

The delivery efficiency of nanoparticulate chemotherapeutics in tumors: another story "of mice and men"

Increased delivery efficiency of nanoparticulate chemotherapeutics has hitherto been predominantly observed in rodent models (**Figure 2**) and has often been attributed to the so-called enhanced permeability and retention (EPR) effect[12] but seldom reported in human nanoparticle therapy experiences. Yet, clinically exploiting the EPR effect has long provided a guideline for the further development of nanoparticulate chemotherapeutics with increased delivery efficiencies, while enduring strong criticism in the drug delivery literature over the past decades[28-35].

The EPR effect is closely associated with the vascular structure and lymphatic drainage in solid tumors. Tumors generally possess disorganized blood vessels[17,36] due to unique tumor metabolic demands and poorly coordinated neo-vasculogenesis that accompanies rapid tumor growth (**Figure 4**). The altered structure of select tumor vasculature *versus* normal tissue vasculature allows 100–200 nm nanocarriers to permeate through vessel walls and gaps in tumor endothelial fenestrations, and enter and become retained more effectively in tumor tissue than in normal tissue. Based on observations in rodent models[13], nanoparticulate chemotherapeutics 50–200 nm in diameter were retained by poor tumor lymphatic drainage, while smaller sizes were removed by lymphatic vessels

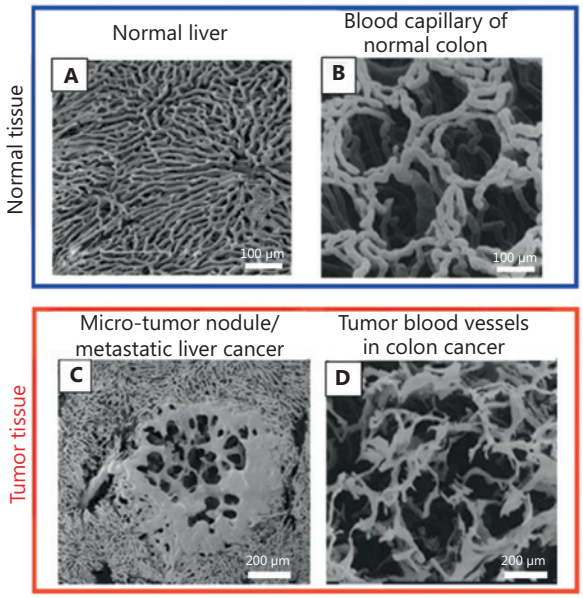


Figure 4 Scanning electron micrographs illustrating structural differences between normal and tumor-associated vasculature in murine tissues[36]. (A) Normal liver tissue showing the highly organized and homogeneous sinusoidal vascular network with a regular, parallel architecture that supports efficient perfusion. (B) Blood capillaries of normal colon displaying a circular, well-defined, and hierarchically organized vascular pattern characteristic of healthy intestinal microcirculation. (C) Micro-tumor nodule in metastatic liver cancer, defined as a small, localized cluster of invading tumor cells surrounded by compressed and remodeled host tissue, associated with profound disruption of the normal hepatic vascular architecture. (D) Tumor blood vessels in colon cancer demonstrating a chaotic, irregular, and severely damaged vascular network, characterized by distorted vessel morphology, loss of hierarchical organization, and features consistent with pathologic angiogenesis. Scale bars: 100 µm (panels A, B) and 200 µm (panels C, D). Adapted under the terms of the CC-BY license[36]. Copyright 2012, Maeda et al., published by Japan Academy.

surrounding a tumor. The current consensus[37] is that nanoparticulate chemotherapeutics exit tumors *via* lymphatic vessels within or surrounding the tumor in a size-dependent manner and not through leaky endothelium. Larger nanoparticulate chemotherapeutics (50–100 nm diameter) exit tumors through lymphatic vessels, which likely enables recirculation and repeated tumor re-entry, increasing delivery efficiency. Whether or not this occurs critically depends on the nanoparticulate chemotherapeutic design and whether nanocarriers have disassembled or released the cargo upon their first entry into the tumor environment.

Human tumors are much more heterogeneous than tumor xenografts used in rodent models and often exhibit dense stroma that counteracts the transport effects of vascular leakiness by physically blocking tumor entry through diffusion[38]. Blood flow in human tumor vessels that may aid re-entry upon lymphatic exit appear absent[39]. As a result, EPR effects observed in humans are modest compared to rodent models[40]. Of the few nanoparticulate chemotherapeutics successfully translated to clinical use to treat human renal and breast cancers[17], added patient therapeutic benefits over free drug therapies have generally been shown to be negligible[28]. A meta-analysis on conventional delivery of carrier-free doxorubicin compared to delivery from PEGylated liposomal nanocarriers in 14 different clinical trials (totalling 2589 patients) demonstrated no significant difference in treatment efficacy[41]. This result sharply contrasts with much more favourable results observed in rodent models[33,40,42,43]. The current general consensus regarding the EPR-effect converges towards an "overpromise" of translational relevance of the rodent tumor model results to the human clinical experience[44].

PPO-tumors

The relatively small, incremental gains in patient longevity obtained over past decades using conventional, systemically injected carrier-free chemotherapeutics taken together have yielded highly meaningful lifetime gains for many different, but not all cancer types[5,8]. Some types of cancer still appear particularly refractory to chemotherapy. Herein, we adopted the term "PPO-tumors" for tumors exhibiting features that reproducibly correlate with poor prognosis outcome across cohorts. PPO-tumors typically differ from better-treatable tumors by rapidly evolving genetic alterations, a highly immune-suppressive microenvironment, effective efflux pumps, resistance to apoptosis and metastatic potential, hypoxia, and thick fibrotic and stromal barriers reducing chemotherapeutic delivery to tumor sites[38,45]. Notable, current PPO-tumors include amongst others pancreatic ductal adenocarcinoma, colorectal carcinoma, and some biliary cancers.

Over the past decade, increasing numbers and diversities of bacterial strains have been identified within different human cancers.[46] For some cancer types resistant to chemotherapeutic treatment, impressively high associations between treatment outcome and bacterial presence in tumors have been shown upon tumor resection or post-mortem analyses[10,47]. This correlation warrants considering bacteria-infected tumors as a special type of PPO-tumor. Further, treatment strategies that specifically and effectively address bacteria-infected tumors represent a new anti-cancer approach.

Hypotheses on PPO-tumors and bacterial infection

Development of novel strategies to treat PPO-tumors according to current clinical paradigms and regulatory approval

procedures is slow, most certainly for patients with PPO-tumors. Therefore, to accelerate further development, we advance three hypotheses with respect to PPO-tumors, knowing the hypotheses are conflicting with present clinical treatment paradigms. To make our hypotheses amenable for debate, hypotheses were formulated unambiguously according to Popper's falsifiability criterion, as follows[48]:

1. all diagnosed PPO-tumors must be considered to be bacteria-infected;
2. all PPO-tumors in mice and men exhibit enhanced permeability to chemotherapeutics; and
3. all diagnosed PPO-tumors must be treated from the onset with a carrier-free antibiotic/chemotherapeutic drug combination. Note that this hypothesis does not argue that all PPO-tumors are bacteria-infected, but rather that current diagnostic limitations may mask a clinically relevant bacterial contribution across multiple tumor types.

Based on a review of the literature, each hypothesis was critically evaluated for plausibility, rejection, and opportunities offered for further elaboration. Evaluation was confined to pancreatic ductal adenocarcinoma, colorectal carcinoma, and some biliary cancers as examples of PPO-tumors.

Hypothesis 1: All PPO-tumors must be considered to be bacteria-infected

This hypothesis has plausible and problematic aspects. In each of the three PPO-tumor types considered here, ample evidence has shown that bacteria exist inside these tumors with multiple, proposed contributions to the PPO-specific character of the tumor (**Table 1**). Different bacterial strains and species listed in **Table 1** have even been described to be diagnostic and prognostic for recurrence or metastasis in head and neck cancers[56]. Overall, these studies make the hypothesis plausible.

Problematically, the mere presence of intratumoral bacteria does not always confer causation. Tumor "aggressiveness" is usually driven by genetics (mutations and epigenetics) and how genetics interacts with the host immune system and TME. Thus, PPO-tumor character is not necessarily driven by bacterial infection[45].

To increase the plausibility of this hypothesis, the consistent presence of bacteria in PPO-tumors need to be established. This requires careful clinical sample collection that can only be accomplished upon tumor resection or post-mortem analyses. Simultaneously, adjacent healthy tissue samples and surgical equipment used should be cultured to rule out possibilities of bacterial contamination during surgical entry and tumor removal, analogous to recommendations for the diagnosis of septic loosening of orthopaedic implants[57]. Subsequent bacterial identification, localization, and load inside tumor cells or stroma must be determined and correlated with tumor grade and stage, responses to chemotherapy or immunotherapies, and patient survival. The plausibility and possible further evidence pave the way for hypotheses 2 and 3.

Hypothesis 2: All PPO-tumors exhibit enhanced permeability to chemotherapeutics

Whether or not human tumor endothelium exhibits enhanced permeability is of crucial importance for the utility of novel, nanoparticulate chemotherapeutics. However, the prevailing consensus that the EPR effect exists primarily in rodents and only rarely in humans, is not necessarily true for bacteria-infected tumors. It is highly plausible that bacteria-infected tumors promote substantially higher leakiness than in uninfected tumors, also in humans, simply because infection-driven vasculature tends to be immature and disorganized, causing vascular leakiness. Importantly, this hypothesis does not imply uniform or universal enhancement of permeability, because fibrosis, interstitial pressure, lymphatic dysfunction, and biofilm formation may locally or globally limit nanoparticle penetration despite bacterial presence. Clinically significant EPR effects in human infections are reported across the major pathogenic bacterial species[58] in which bacterial toxins and metabolites disrupt tight junctions, and excessive ROS generation due to increased immune infiltration further damages endothelium. Therefore, intratumoral bacteria amplify permeability, enabling EPR effects, also in humans. At the same time, it must be realized that the EPR effect is not simply about leakiness but also relies on active tumor lymphatic drainage, interstitial pressure, and whether bacteria-induced fibrosis hinders deep penetration[59,60]. In addition, heterogeneous tumor regions are not affected equally by bacterial presence and infectious bacterial biofilms represent barriers that hinder penetration of nanoparticulate chemotherapeutics into a tumor[61,62].

Currently, some studies appear to indicate that intratumoral bacteria presence helps tumor penetration of nanoparticulate chemotherapeutics. *Salmonella*-based tumor therapies have shown that bacteria can increase vascular permeability for drug delivery[63] and animal experiments with bacteria/nanoparticle combinations have shown increased penetration, suggesting that bacteria modulate the microenvironment to facilitate penetration[64,65]. Unfortunately, systematic studies comparing nanoparticle delivery in sterile *versus* infected tumor models are lacking, to which end animal models with a bacterial colonization like that in human tumors would be useful.

The discussion on whether EPR-effects primarily exists in rodent models and not in human tumors, has not slowed down development of nanocarriers dual-loaded with antibiotic/chemotherapeutic combinations to treat bacteria-infected tumors. Therefore, nanotechnology seems to have accepted hypothesis 2. As an example, stimuli-responsive liposomes dual-loaded with an antibiotic and a chemotherapeutic[66]

Table 1 Bacterial strains and species found in pancreatic ductal adenocarcinoma, colorectal carcinoma, and biliary tract cancers, together with the contribution to the PPO-character of a tumor. Foundational references were author-selected and verified.

Bacterial strain/species	Contribution to PPO-tumor characteristics
Pancreatic ductal adenocarcinoma (foundational references[49-51])	
Bacteroides fragilis	Possible inflammatory role; Linked to chemoresistance; Altered immune and cell apoptosis pathways
Escherichia spp.	Linked to chemoresistance; Altered immune and cell apoptosis pathways
Enterobacteriaceae spp.	Metabolizes gemcitabine
Enterococcus faecalis	Metabolizes gemcitabine and 5-fluorouracil
Fusobacterium nucleatum	Promotes immune evasion and chemoresistance
Helicobacter pylori	Tumor cell invasion and metastasis
Klebsiella spp.	Linked to chemoresistance; Altered immune and cell apoptosis pathways
Pseudomonas spp.	Metabolizes gemcitabine
Salmonella spp.	Linked to chemoresistance; Altered immune and cell apoptosis pathways
Streptococcus spp.	Possible inflammatory role
Colorectal carcinoma (foundational references[51-53])	
Bacteroides fragilis	Produces toxins that drive inflammation and carcinogenesis
Clostridium spp.	Linked to altered immune pathways
Escherichia coli	Activation of inflammatory signaling cascades; Cancer cell detachment and survival; Linked to biofilms and gallstone formation
Fusobacterium nucleatum	Promotes immune evasion and chemoresistance
Parvimonas micra	Association with CRC progression
Peptostreptococcus anaerobius	May drive cell proliferation
Streptococcus gallolyticus	Genetic and epigenetic alterations in protooncogenes, genes that affect DNA repair mechanisms, or tumor suppressor genes
Biliary tract cancers (foundational references[54,55])	
Clostridium spp.	Contributes to bile duct inflammation
Enterococcus spp.	Associated with potentially toxic secondary bile acid; Contributes to bile duct inflammation
Helicobacter bilis, *H. pylori*	Contribute to inflammation and DNA damage
Salmonella typhi	Elevates gall bladder cancer risk

yielded 20-fold enhanced delivery of gemcitabine to bacteria-infected tumors in a rodent model compared to conventional delivery of carrier-free gemcitabine alone and >2-fold higher efficacy compared to gemcitabine delivery co-administered with carrier-free ciprofloxacin (**Figure 5A**). Furthermore, ciprofloxacin delivery from liposomes was roughly 2-fold higher that when co-delivered as a carrier-free drug together with gemcitabine (**Figure 5B**). Both *E. coli* presence in tumor tissue (**Figure 5C**) as well as tumor weight (**Figure 5D**) decreased significantly, which was consistent with increased tumor delivery efficiencies of both ciprofloxacin and gemcitabine, respectively. From the clinical perspective, closer

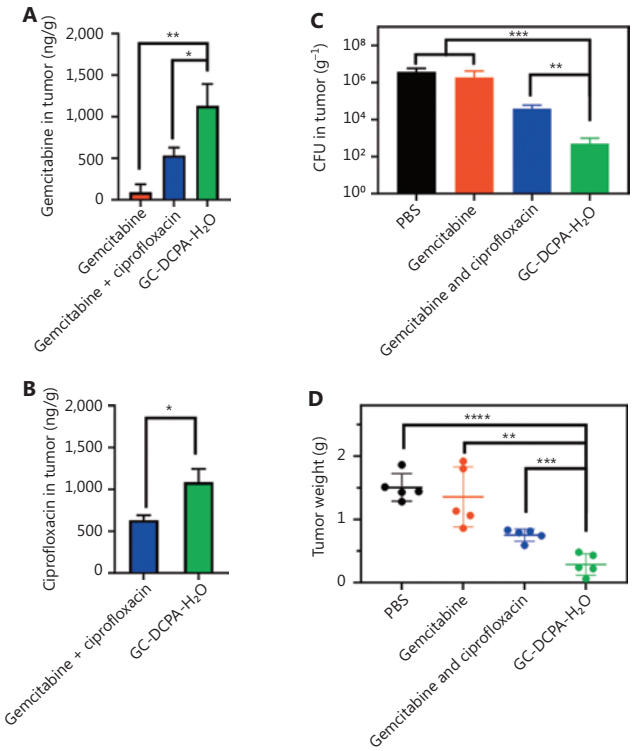


Figure 5 Tumor delivery, antibacterial efficacy, and therapeutic outcome following systemic administration of gemcitabine and ciprofloxacin in a murine *E. coli*-infected colorectal carcinoma model[66]. Animals received tail-vein injections of either carrier-free gemcitabine and ciprofloxacin or stimuli-responsive GC-DCPA-H_2O liposomes co-loaded with ciprofloxacin and gemcitabine[66]. (A) Gemcitabine concentration in tumor tissue, demonstrating enhanced intratumoral drug accumulation following co-delivery, most notably upon co-delivery from the responsive liposomal formulation. (B) Ciprofloxacin concentration in tumor tissue, indicating enhanced intratumor antibiotic concentrations following co-delivery, most notably upon co-delivery from the responsive liposomal formulation. (C) The number of bacterial colony-forming units (CFUs) per gram tissue excised from the solid tumor at sacrifice (day 16), reflecting the antibacterial efficacy of the different treatment strategies. (D) Tumor weight at sacrifice (day 16), serving as an integrated measure of therapeutic outcome combining anti-tumor and antibacterial effects. Figure used with permission from the publisher. Adapted under the terms of the CC-BY license[66]. Copyright 2023, Wang et al., published by Wiley.

inspection of these results (**Figure 5**) reveals that the added therapeutic benefits of antibiotic/chemotherapeutic delivery from stimuli-responsive liposomes, while statistically significant, is generally small compared with conventional administration of an antibiotic combined with a chemotherapeutic as two carrier-free drugs. This highlights the need for further research to develop stimuli-responsive nanocarriers with several fold higher delivery efficiencies than hitherto realized.

Hypothesis 3: All diagnosed PPO-tumors should be treated from the onset with a carrier-free antibiotic/chemotherapeutic drug combination

Given the absence of accepted, clinically applicable methods to readily diagnose bacterial infection of solid tumors, this hypothesis conflicts with clinical paradigms of infection treatment, as well as with increasing clinical demands to avoid antibiotic resistance. Despite the plausibility that all or at least many PPO-tumors may well be bacteria-infected (hypothesis 1), the absence of diagnostic options to confirm infection impedes both rationale selection and implementation of appropriate antibiotic/chemotherapeutic combinations to routinely treat PPO-tumors as being infected.

On the individual patient level, antibiotics may adversely affect the host's protective oral and gut microbiomes[67,68]. However, antibiotic use in cancer patients is common, particularly when chemotherapy compromises the host immune status, and/or when treatment involves intravascular catheterization or biliary stents that are both prone to biomaterial-associated infection[69]. Potential negative impacts of antibiotic use on protective microbiota can be managed/reduced by probiotic and prebiotic administration[70]. On a more global scale beyond individual patients, the impact of such cancer-based antibiotic use

in critically ill cancer patients on further development of antibiotic resistance seems negligible compared to the risks of current excessive over-the-counter promotion, use, and abuse of unnecessary antibiotics occurring in many countries worldwide[70].

Select publications provide indications of possible benefits of adopting hypothesis 3 in animal models as well as in human cancer treatment. For example, antibiotic treatment before administration of chemotherapeutics proved beneficial for restoring chemotherapeutic sensitivity in mice and men. Studies have suggested antibiotic targeting of *Helicobacter pylori* bacteria in pancreatic ductal adenocarcinoma before administration of chemotherapeutics restored gemcitabine sensitivity in rodent models[66,71]. In human patients with benign familial adenomatous polyposis, 70% of patients harboured bacteria in colon specimens, while in a group of patients treated with antibiotics for 24 h before surgery, no colon specimens were found harbouring bacteria, suggesting that antibiotics effectively prevented tumor bacterial colonization[72,73]. Metronidazole and ciprofloxacin have shown mixed effects for enhancing chemotherapy in colorectal cancers[65,74]. The conventional combined administration of ciprofloxacin- and gemcitabine-free drugs to infected murine solid tumors showed re-sensitization of tumors to chemotherapeutics with significant anti-tumor effects[71] (**Figure 6**), which was similar to what was observed for stimuli-responsive GC-DCPA-H_2O liposomes co-loaded with ciprofloxacin and gemcitabine (**Figure 5**).

The above considerations indicate that hypothesis-based administration of combinations of carrier-free antibiotic and chemotherapeutic-free drugs may provide an immediate pathway to re-sensitize PPO-tumors to clinically used chemotherapeutics and yield a significant gain in clinical outcomes for patients with PPO-tumors.

Conclusions

Figure 7 presents a conceptual summary of the rationale leading to the conclusions of this review. After decades of advances in cancer treatment, progress is stalling for a sub-set of tumors (**Figure 7A and 7B**, respectively). Research, production of new nanoparticulate chemotherapeutics with higher efficacy than the clinically used carrier-free drug analogues focuses on reducing off-targeting (**Figure 7C**), but translation from mice to men (**Figure 7D**) remains troublesome yet scientifically challenging. Despite many optimistic claims otherwise, it is unlikely that this situation will radically change anytime soon to provide a readily translatable and broadly applicable new anti-cancer strategy[75].

Considering the typically short treatment windows available and high mortality rates of patients with PPO-tumors, the authors' expert opinions are that, based on current evidence available, all PPO-tumors should, per hypotheses (**Figure 7E**), be considered as bacteria-infected and treated from the onset with conventional administration of a combination clinically familiar, carrier-free antibiotics and chemotherapeutics, while acknowledging the general need for restrained and justified use of appropriate antibiotics. Clinical benefits of this paradigm change and accompanying treatment proposal (**Figure 7F**) should be subject to retrospective clinical verification.

It is important to realize that clinical therapeutic innovation can only occasionally be validated within the constraints of randomized cross-over, double-blind, prospective clinical trials. In the clinical evidence pyramid[76] (**Figure 7G**) such trials are recognized as high quality, but expensive, tedious, and time-consuming, and hence rarely performed to produce decisions that truly affect patient care. Hence, we

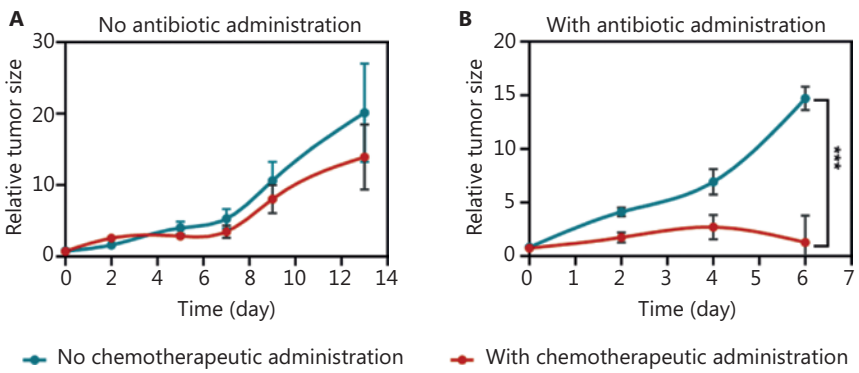


Figure 6 Effects of combined, free antibiotic and chemotherapeutic treatment on tumor growth in a murine *E. coli*-infected colorectal carcinoma[71]. Data are expressed relative to the tumor size at day 0. (A) Absence of significant differences in infected tumor size normalized to tumor size on day 0 between untreated mice and mice treated with gemcitabine in a carrier-free form in the absence of ciprofloxacin, indicating limited anti-tumor efficacy of chemotherapy alone under infection-associated conditions. (B) Significant inhibition of infected tumor growth between mice after co-administration of ciprofloxacin and gemcitabine in carrier-free forms and mice treated with carrier-free ciprofloxacin in the absence of gemcitabine, highlighting the therapeutic benefit of combined antibacterial and chemotherapeutic intervention[71]. Reproduced with permission from Geller et al.[71]. Copyright 2017, American Association for the Advancement of Science.

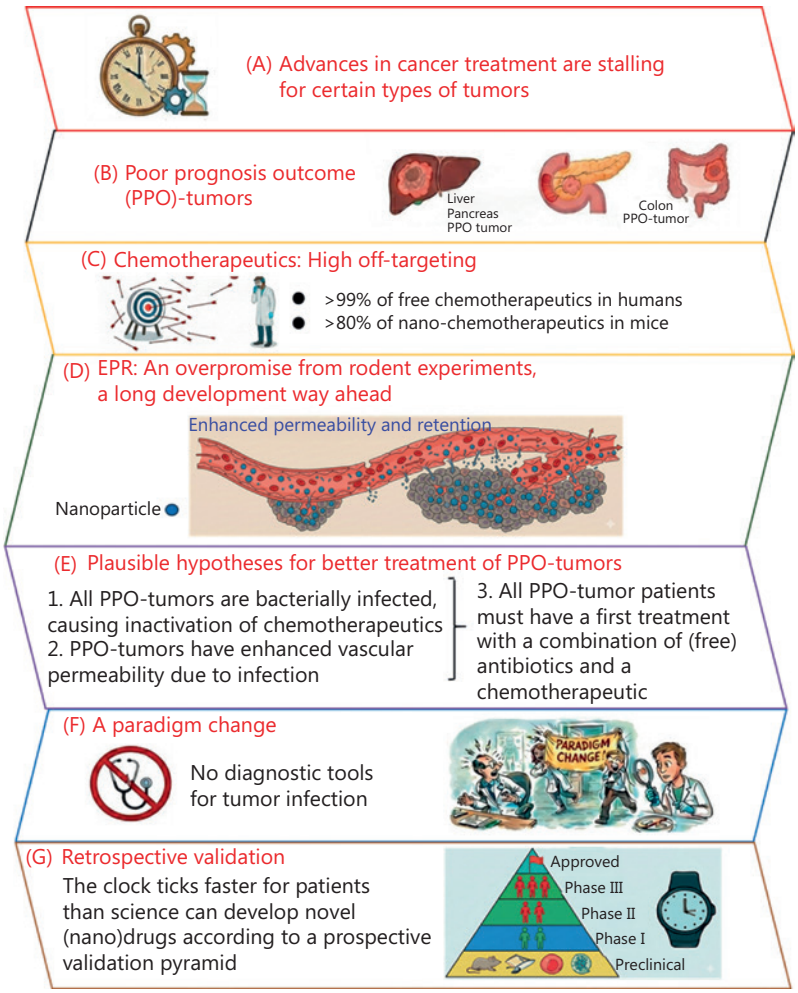


Figure 7 Conceptual summary of the rationale, hypotheses, and proposed paradigm change underlying this review. (A) Despite major advances in targeted therapies, immunotherapies, diagnostics, and supportive care, progress in cancer treatment has stalled for a subset of tumors with persistently poor prognosis outcomes. (B) These cancers are collectively referred to here as PPO-tumors, reflecting the limited responsiveness to current standard-of-care therapies. (C) Systemically administered chemotherapeutics exhibit substantial off-target distribution with >99% of molecular drugs and >80% of nanoparticulate formulations failing to reach the tumor site, contributing to limited efficacy and adverse side-effects. (D) Although enhanced permeability and retention (EPR) has been widely invoked to explain nanoparticle intratumor accumulation, the clinical relevance remains inconsistent, and reliance on further optimisation based on preclinical models may delay meaningful therapeutic advances. (E) Based on a synthesis of the oncologic, microbiologic, and nanomedicinal current evidence, three interrelated hypotheses are formulated to determine whether bacterial presence within PPO-tumors may contribute to chemotherapeutic inactivation, altered vascular permeability, and treatment recalcitrance. (F) Collectively, these hypotheses motivate a paradigm change in which PPO-tumors are considered presumptively bacterially infected in the absence of reliable diagnostic tools, opening the possibility of early carrier-free antibiotic–chemotherapeutic combination treatment. (G) Given the urgent clinical need and the absence of feasible prospective diagnostic strategies, retrospective clinical validation is proposed as a pragmatic pathway to assess the translational relevance of this paradigm for patients with PPO-tumors.

should acknowledge that retrospective clinical verification can sometimes be the only pathway to clinical progress. For example, clinical acceptance of antibiotics has been accelerated by a high number of wounded soldiers to prevent them from dying of infection, while COVID 19 vaccine developments have been accelerated by the huge global impact of the disease. In fact, among many widely accepted therapies lacking randomised prospective clinical trial validation, no randomized cross-over, double-blind, prospective trial has ever been carried out to demonstrate that water intake is thirst-quenching.

Addressing new approaches to treat patients dying of PPO-cancers according to standard randomized cross-over, double-blind, prospective clinical trials that can only occur after

development of clinically applicable, validated tumor diagnostic methods is a far too lengthy process to address this desperate cancer patient population. Many current chemotherapy patients already receive antibiotics to address an array of intrinsic infection risks, yet none acknowledged to be intratumoral, indicating that the paradigm change in clinical therapy practice proposed in the perspective article is in fact already well-accepted.

Epilogue

Author Henk J. Busscher wishes to dedicate this paper to the memory of Joop Behrends, who fiercely fought against pancreatic cancer. When his tumor was finally considered untreatable and inoperable, H.J.B. suggested treatment with a combination of carrier-free, routinely used ciprofloxacin and gemcitabine free in solution. His oncologist agreed and after treatment, his tumor was considered operable. He died three months after surgery. Whether the combined treatment provided him additional time or not, we will never know.

Author contributions

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Conflict of interest statement

H.J.B. is also director of a consulting company (SASA BV). The authors declare no potential conflicts of interest with respect to authorship and/or publication of this article. Opinions and assertions contained herein are those of the authors and are not construed as necessarily representing views of the funding organization or their respective employer(s).

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