



Systemic Administration of Drag Reducing Polymers to Hinder Metastasizing

Pinkowski A* and Lilienblum W*

Abstract

Tumor cells need an extra nutrition supply to survive and grow. Circulating tumor cells (CTC) search for settling down and growing favorable sites in this respect in the blood or lymphatic system. The attachment of CTC tends to occur at sites with local turbulence since in turbulent flow the mass transfer and hence nutrition supply is enhanced. Drag reducing polymers (DRP) have the potential to smooth out (laminarize) local vortices. Intravenous injection of blood soluble non-toxic DRP solutions in nanomolar concentration has been proved to reduce the risk of metastasizing in animal models. It is proposed to apply this approach also for newly detected cancers and as accompaniment of traditional cancer treatments.

Keywords: systemic administration of drug reducing polymers, hemodynamics, metastasis, cancer after care

Introduction

The fact that some polymers, even in very low concentrations, are able to reduce pipe friction was discovered by [1] (Toms effect). Modern additives can reduce friction by up to 80 % [2]. For the fundamentals of drag reduction cf. [3]. A comprehensive review is given by Gu et al., 2020. The human blood and lymphatic systems serve as transport media for circulating tumor cells (CTC). The goal of the present contribution is to promote the idea that systemic administration of nontoxic blood soluble drag reducing polymers (DRP) in nanomolar concentrations should be studied intensively to become a standard complementary cancer treatment.

Since blood rheology is non-Newtonian (non-linear *shear stress-shear rate relation*) one has to apply a threshold force, the yield stress, before blood moves at all. This property is due the blood composition and the particular properties of its components. Blood consists mainly of plasma (with near Newtonian flow behavior) and red blood cells (RBC). This leads to a two-phase flow pattern with the *plasma as carrier phase* and the RBC as carried phase. The RBC are like liquid droplets suspended in plasma. At low velocity gradients, i. e., at low shear rates, RBC tend to form rouleaux structures which are potential sources of vortices. Low shear rates may also cause the primary, randomly scattered rouleaux to group together and create secondary rouleaux [4], cf. Fig. 1. This explains together with the fibrinogen adhered to the vessel wall and to the rouleaux fibrinogen filaments the increased viscosity at low shear rates and also the yield shear stress. Thus arises a slip between plasma and the rouleaux-fibrinogen cluster which causes strong local vortices even in the absence of fully developed turbulent flow.

Affiliation:

*Corresponding author:

Pinkowski A, African Centre of Excellence in Bioinformatics (ACE-B), USTTB, Bamako, Mali.

Citation: Pinkowski A, Lilienblum W. Systemic Administration of Drag Reducing Polymers to Hinder Metastasizing. Journal of Pharmacy and Pharmacology Research. 8 (2024): 66-78.

Received: November 16, 2024

Accepted: November 22, 2024

Published: December 21, 2024

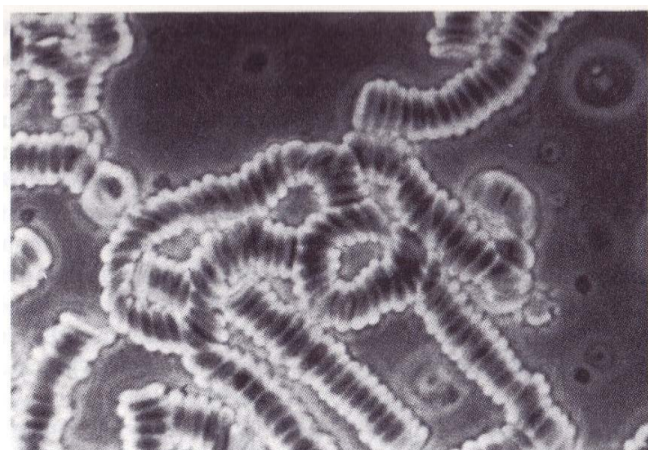


Figure 1: Secondary RBC Rouleaux (Kulicke, 1986)

Low shear rates occur also in tumor vessels and may facilitate rouleaux formation even at low hematocrit values [5].

Blood flow is laminar below Reynolds numbers $Re \approx 2300$ and it becomes turbulent for $Re > 3000$ (1)

$$Re = 2Rvp/\eta \quad (1)$$

with R = vessel diameter

v = mean blood velocity (mean in time and cross-section)

ρ = whole blood density,

and η = dynamic viscosity

Turbulent blood flow may occur where the local vessel diameter is reduced as in arterial stenosis which results in locally increased blood flow velocity. Low blood viscosity η , as occurs in anemia (low RBC content), also promotes turbulence. Further, vessel branching (bifurcation) and vessel bending with plasma skimming [6] may also lead to local turbulence; Generally, in turbulent blood flow the parabolic velocity profile becomes blunted. It is known that atherosclerotic lesions of blood vessels are not randomly distributed but tend to occur at sites with disturbed laminar blood flow, as at vessel bifurcations. Even in a healthy circulatory system this may cause endothelial lesions due to flow-induced apoptosis. Such lesions are potential docking points for metastasizing tumor cells.

Apart from branching and curving, vessel dilatation above critical Reynolds numbers may cause blood pooling in the low shear environment near the internal wall of blood vessels. Thus, a vicious cycle can develop where increased blood viscosity leads to decreased flow which in turn increases viscosity even more and decreases flow further, culminating in stasis and thrombosis.

RBC tend to accumulate in the vessel center, leaving the RBD-depleted plasma in the wall region reducing thus the blood viscosity in the near wall region. This way the near-wall velocity profile becomes steeper while it becomes smaller in the vessel center with the risk of fibrinogen-aided

RBC rouleaux formation. The risk of cluster is enhanced in cases of impeded circulation since the cluster formation time is about 10 seconds, i.e., about 10 times higher than the heart pulse time [7]. In a preprint, a peer-reviewed paper and finally a book chapter a hypothesis was proposed that systemic administration of drag reducing polymers (DRP) may reduce the risk of metastasizing after cancer surgery [8-9]. Further it was proven experimentally that this type of intervention drastically reduces the extravasation and development of pulmonary metastasis of human breast cancer cells in mice [10]. A patent has been filed claiming a hemorheologic approach for reduction or prevention of cancer metastasis formation [11]. Moreover it was shown experimentally that drag reduction may inhibit tumor growth in its first stage of development or even lead to starvation-induced death of first tumor settlements [12].

Although it is not explicitly known which geometric shape PEO additives injected into the human circulation adopt, it seems reasonable to assume that they dissolve in the blood and create long polymer chains that interact with turbulent flow, damping thus the energy of eddies. The polymer chains are flexible, and by coiling and stretching in response to the flow, they minimize turbulence and reduce drag. **Kulicke (l.c.)** explains that linear polymers are chain- or thread-shaped molecules that take on the shape of a coil in a dilute solution. Under the influence of statistical thermal motion, the coil shape is constantly changing. On average over time, such a polymer coil takes on the shape of a bean-shaped ellipsoid.

DRP used as drag reducing additives degrade under turbulent flow. When subjected to elevated levels of shear and turbulence, the polymers break down and lose effectiveness due to mechanical degradation. The degradation is caused by the intense stress that turbulent eddies place on the long-chain molecules and causes them to break into smaller fragments. Rather than forming a specific geometric shape, PEO molecules reduce drag through their molecular structure and flexibility. Their elongated and entangled nature allows them to align with the flow and to reduce thus local turbulence. When injected into the human circulation DRP have a service lifetime of 2 or 3 days and have to be re-injected to keep effectiveness. Tumor cells need extra nutrient supply to survive and grow. The settling down of CTC in the circulatory system tends therefore to occur at sites with localized turbulence since in turbulent flow the mass transfer, and hence the nutrient supply, is enhanced. A recent article defines the hydrodynamic conditions for laminar, transitional and turbulent pathophysiological blood flow [13]. Whatever extravasation mechanisms of CTC may be active it is always preceded by a settle down step. CTC are smart enough to search for sites with a favorable nutrition supply as part of their survival strategy. DRP in extremely low concentrations are known to laminarize local turbulences. Therefore, a

systemic administration of DRP in nanomolar concentrations as complementary post-operative cancer aftercare to minimize the risk of metastasizing is promising. The better flowability of blood after intravenous injection of DRP may even serve to substitute Heparin to treat and prevent blood clots [14].

While earlier proposals focused on avoiding metastasizing *after* cancer surgery, the same reasoning should also be valid for cancers *before* surgery, i. e., for primary and non-operable cancer types.

The idea of starving cancer cells after the settling-down process, i. e., cutting off their energy supply or disrupting their metabolism, like glucose restriction, amino acid deprivation, inhibition of lipid metabolism or autophagy inhibition have been proven to be only partly successful since cancer cells are able to alter their metabolic processes.

The laminarizing DRP action before settling down of CTC will increase their circulation time which in turn will allow the body's own defense to kill the CTC. The fate of CTC in the body depends on several factors, including their ability to evade the immune system, survive in the bloodstream, and set up metastases. There is no specific fixed time for how long CTC can circulate before being cleared by the body. Their lifespan can vary widely depending on some of the following circumstances:

Immune System Activity

The immune system is constantly working to detect and destroy abnormal cells, including CTC. Many CTC are eliminated within hours or days by immune cells, i. e., by natural killer cells.

Shear Stress in the Bloodstream

The turbulent flow of blood exerts mechanical forces on CTC, which can destroy them. Many CTC are cleared within hours to days.

CTC Characteristics

Some CTC are more resistant to immune destruction and mechanical stress. These cells may survive longer in circulation and eventually exit the bloodstream to form metastases.

Organ Trapping

CTC may become trapped in capillaries, especially in organs like the liver, lungs, or bone marrow. If they fail to colonize these organs, they may die or be removed by the immune system. The overall circulation time can therefore range from minutes to days. Only in cases where CTC are able to survive longer, can they eventually leave the bloodstream and establish new metastatic tumors. Although there are several cancer research centers worldwide that focus on metastasis, these institutions aim primarily to understand

the mechanisms behind metastasis and develop targeted therapies. Research areas are how cancer cells spread, interact with other organs and settle in distant organs.

Targeting Metastasis-Specific Genes and Pathways: For example, exploring the inhibition of enzymes like matrix metalloproteinases that break down the surrounding tissue, allowing cancer cells to invade new areas, cf. [15].

Blocking the Tumor Microenvironment: Tumor cells often rely on signals from their surrounding environment (stroma) to support their growth and spread. Disrupting this microenvironment makes it less favorable for cancer cells to survive and spread. This includes targeting fibroblasts, immune cells, and other cells that support the tumor, cf. [16].

Preventing Angiogenesis: Metastatic tumors require a blood supply to grow in new locations. Anti-angiogenic drugs, like bevacizumab (Avastin), aim to prevent new blood vessel formation, starving metastatic tumors of nutrients and oxygen, cf. [17].

Immunotherapy to Target Metastasis: Advances in immunotherapy, such as checkpoint inhibitors and CAR-T cells, show potential in preventing metastasis by boosting the immune system's ability to detect and destroy spreading cancer cells, cf. [18].

Inhibiting Epithelial-Mesenchymal Transition (EMT): EMT allows epithelial cancer cells to gain the mobility and resilience of mesenchymal cells, aiding metastasis. Research focuses on drugs to block EMT, cf. [19].

Drug Repurposing: Some non-cancer drugs, like beta-blockers and statins have the potential to inhibit metastasis, because they interfere with stress signaling and cholesterol pathways that help cancer cells survive and spread, cf. [20].

Drag-reducing polymers (DRP), like polyethylene oxide (PEO), have been found to reduce the survival and spread of CTC due to altering blood flow characteristics, like the interaction of CTC with the bloodstream and vascular walls.

Some research insights into this approach are:

Shear Stress Increase: DRP increase the blood flow velocity and shear rates within vessels, especially in smaller arteries and capillaries. Higher shear stress has been shown in studies to induce apoptosis in certain types of cancer cells, thereby reducing their ability to survive and form secondary tumors.

Impact on CTC Adhesion: CTC adhere to the endothelial lining to exit circulation and invade surrounding tissues. By changing the flow profile, DRP hinder CTC from coming close enough to vessel walls to adhere effectively, reducing the likelihood of extravasation into distant tissues, cf. [21].

Enhanced Immune Clearance: Increased blood flow

velocity due to DRP exposes CTC to immune cells in circulation more often, improving the chances of immune cells identifying and clearing CTC, cf. [21].

Side Effects and Hemodynamics: DRP can alter oxygen transport and cardiovascular stress due to modified blood viscosity. Studies focus on dosing and delivery mechanisms to avoid negative systemic effects, cf. [22].

Other studies concerning metastasis focus on:

The role of *PI3K/Akt/PTEN/mTOR signaling pathway*, autophagy, epithelial-mesenchymal transition and cancer stem cells in metastatic processes and radioresistance of prostate cancer, as well as preclinical studies on treatments combining radiosensitizers and radiotherapy, cf. [23]. Conducted on a mouse model, another study suggests that the development of breast cancer would be the result of a metastatic process emanating from a renal tumor, cf. [24]. A review article treats the prospects of targeting the Ras-ERK signaling pathway for the treatment of pancreatic ductal adenocarcinoma, cf. [25].

Further the role of mesenchymal-epithelial transition in the metastatic process of breast cancer is treated, cf. [26].

An overview treats interventional trials on CTC in breast cancer, cf. [27].

Polyethylene oxide in food and drugs

The most used DRP is polyethylene oxide (PEO), also known as polyethylene glycol when it has a lower molecular weight, is used in food and pharmaceutical products as a food additive, mainly as a thickening agent, stabilizer, or emulsifier. Its use is regulated, and the allowable percentage depends on the specific application and local regulatory frameworks. The Food and Drug Administration (FDA) recognizes certain forms of polyethylene glycol as "Generally Recognized As Safe" (GRAS) for use in food. In the European Union, polyethylene glycol is listed under certain E-numbers. Its use as a food additive is allowed in certain applications; The allowed percentage depends on the food category. Generally, it is used in minimal amounts in food products like in coatings and capsules.

Simultaneous administration of anti-cancer drugs and DRP

The usefulness of a simultaneous administration of anti-cancer drugs and DRP depends on the way the drugs target the cancer, and it is easiest imaginable with water soluble drugs. Many anticancer drugs are formulated as aqueous solutions for intravenous injection or infusion. These solutions allow for easy and quick absorption into the bloodstream, ensuring rapid systemic distribution. Examples are: 5-Fluorouracil, which is often prepared in aqueous form, and Doxorubicin, administered as an aqueous solution for intravenous infusion.

The frequency of injectable cancer drugs depends on several factors, including the type of cancer, the specific drug being used, the stage of the disease, and the patient's overall treatment plan. Typical drugs given once a week are paclitaxel, methotrexate and trastuzumab. Weekly regimens are often used to minimize side effects and allow the patient's body to recover between treatments. Doxorubicin or pembrolizumab, an immunotherapy drug, may be administered every two or three weeks. This schedule gives the body more time to recover between treatments.

* Bevacizumab or some immunotherapy drugs like nivolumab are given on a monthly basis. This schedule is common for maintenance therapies where long-term management of cancer is the goal, cf. [28].

Most chemotherapy and immunotherapy regimens are administered in cycles, meaning a set number of doses followed by a rest period. A common cycle might be 3 weeks (e.g., treatment on day 1, followed by two weeks of rest) or 4 weeks, depending on the drug and patient tolerance. *

Some treatments, e.g., 5-fluorouracil, are delivered via a continuous infusion over several days and may require a portable infusion pump.

Factors that influence the frequency of applications depend on the cancer type, and the drug type. Chemotherapy, immunotherapy, or targeted therapy drugs have different dosing schedules. Dosing and frequency are adjusted based on how well a patient tolerates the drug, and on the treatment goals. Curative treatments may be more intense, while palliative treatments could have less frequent dosing. Generally, for the proposed joint intravenous treatment best a cancer drug which is administered weekly is suitable due to the restricted lifetime of DRP in the circulatory system which is about 2 or 3 days. Although surgery is a common treatment choice for many types of cancer, certain cancers cannot be treated effectively with surgery due to their location, stage, or biological characteristics. Cancer types that are generally considered difficult or unsuitable for surgical treatment are

Blood Cancers (Leukemia and Lymphoma)

Leukemia affects the blood and bone marrow, which are dispersed throughout the body. Because it is not localized to a specific tumor or area, surgery is not effective. Lymphomas, especially those involving widespread lymph nodes or bone marrow, are generally treated with chemotherapy, immunotherapy, or radiation instead of surgery, cf. [29].

Advanced-Stage Cancers or Metastatic Cancers

When cancer has metastasized to distant organs or tissues, surgery to remove the primary tumor may not be helpful. In these cases, systemic treatments like chemotherapy, targeted therapy, or immunotherapy are more effective for managing the disease throughout the body.

Pancreatic Cancer (Inoperable or Late-Stage)

Pancreatic cancer is often diagnosed at a late stage when it has spread to surrounding blood vessels or other organs, making surgery risky or ineffective. Even in earlier stages, pancreatic tumors may be difficult to remove completely due to the location of vital structures.

Brain Cancers (Certain Gliomas and Glioblastomas)

Some brain tumors, such as glioblastomas, grow in regions that are difficult to access or too integrated with essential brain tissue, making complete surgical removal impossible. In these cases, other treatments like radiation or chemotherapy may be prioritized, though surgery can still be part of a broader treatment plan, cf. [30].

Lung Cancer (Advanced-Stage or Non-Operable)

For many patients with advanced lung cancer (Stage III or IV), surgery is often not recommended because the cancer has spread beyond the lungs or because of the patient's poor overall health or lung function. Targeted therapies, immunotherapy, or radiation are therefore often used instead.

Mesothelioma

Mesothelioma, a cancer that affects the lining of the lungs or abdomen (caused by asbestos exposure), is often diagnosed at an advanced stage. It may be too widespread for surgery, and the location of the tumors near delicate organs makes it risky. Treatment often involves chemotherapy and immunotherapy.

Esophageal Cancer

In advanced stages of esophageal cancer, when the cancer has invaded nearby organs or lymph nodes, surgery may not be a practical option. Alternative treatments like chemotherapy, radiation, or stents to keep the esophagus open may be used instead.

Liver Cancer (Multiple Lesions or Cirrhosis)

Surgery may not be possible if the cancer has spread to multiple parts of the liver or if the patient has liver cirrhosis, which limits the ability to safely remove part of the liver. Other options like ablation, embolization, or liver transplantation might be considered, cf. [31].

Ovarian Cancer

While early-stage ovarian cancer can be treated surgically, in advanced stages, the cancer may have spread extensively within the abdomen, making complete removal impossible. Surgery might be followed by chemotherapy, or chemotherapy may be the primary treatment, cf. [32].

Prostate Cancer

In advanced prostate cancer, especially when it has

metastasized bones or lymph nodes, surgery is not typically effective. Hormone therapy, chemotherapy, or radiation therapy are more common treatments, cf. [19].

Head and Neck Cancers

Some cancers in the head and neck region may be inoperable if they are in locations that make surgery too dangerous or if they have spread into areas where complete removal is not possible. Radiation and chemotherapy are often used as primary treatments, cf. [33].

Cancers with Extensive Lymph Node Involvement

Breast cancer or gastric cancer may not be surgically treatable if they have spread extensively to lymph nodes. In these cases, surgery may be combined with systemic treatments like chemotherapy, or chemotherapy alone may be applied, cf. [34].

Certain Soft Tissue Sarcomas

Some soft tissue sarcomas, especially those in difficult-to-reach areas or with large and diffuse tumor growths, may be too challenging for surgery. Radiation and chemotherapy are often the preferred treatment, cf. [35].

In summary, cancers that are widespread, in critical or difficult-to-reach locations, or are blood-based generally cannot be cured or managed effectively through surgery. For these cancers, systemic treatments like chemotherapy, radiation therapy, targeted therapy, or immunotherapy are often more appropriate. In these cases, the proposed systemic administration of DRP cannot be combined but could be applied separately.

Starving cancer cells

An alternative treatment starving cancer cells to death has been proposed. Starving cancer cells or cutting off their energy supply or disrupting their metabolism has been therefore explored in various scientific studies. Some cancer cells are highly dependent on glucose for energy. By restricting glucose availability, one has found that these cells can be weakened or killed. However, this approach is complicated by the fact that normal cells also need glucose, so targeting cancer cells specifically is challenging. One has used glycolysis inhibitors to block glucose metabolism in cancer cells, which has shown promise in preclinical models, i. e., in lab-based studies and animal models. For instance, drugs like 2-deoxyglucose have been studied to disrupt glucose metabolism in tumors. Further a ketogenic diet (low-carbohydrate, high-fat diet) has been proposed to starve cancer cells of glucose while providing alternative energy sources (like ketones) that normal cells can use more efficiently than cancer cells. Some preclinical and animal studies have demonstrated that a ketogenic diet could slow the growth of certain types of tumors by reducing glucose levels in the bloodstream.

Another starving approach focuses on amino acid deprivation since certain types of cancer cells are highly dependent on specific amino acids for survival. For example, certain leukemias are dependent on asparagine or arginine for growth. By targeting these amino acids, e.g., by using enzymes like L-asparaginase to deplete asparagine, one has managed to starve cancer cells selectively. Enzyme-based therapies, such as L-asparaginase, have been used in the treatment of acute lymphoblastic leukemia and have demonstrated that depriving cancer cells of certain amino acids can be an effective therapeutic strategy. Cancer cells also rely on lipids for energy and membrane synthesis. Some research focuses on inhibiting lipid metabolism to block cancer cell growth and proliferation. Drugs targeting fatty acid synthesis and oxidation are in development and preclinical testing showing promise in disrupting cancer cell metabolism. Cancer cells sometimes rely also on autophagy, which allows them to break down and recycle components when under stress, including during nutrient deprivation. Inhibitors of autophagy, like chloroquine and hydroxychloroquine have been tested in combination with chemotherapy showing an increased sensitivity of cancer cells to treatment. Concluding on can say that there is some evidence from experiments, particularly in animal models and cell cultures, that starving cancer cells can hinder their growth or kill them, this approach is still in the experimental stages for most cancers, and clinical success has been limited to specific contexts like amino acid deprivation in leukemia.

Facts about polyethylene oxide

The most used DRP is polyethylene oxide (PEO) also known as polyethylene glycol (PEG) in low molecular weight form. PEO and PEG are chemically identical, but differ in molecular weight. The chemical structure of both consists of repeating units of the monomer ethylene oxide ($-\text{CH}_2\text{CH}_2\text{O}-$). The term PEG is used for polymers with a molecular weight below 20,000 g/mol (or Da). The term PEO refers to polymers with a molecular weight above 20,000 Da up to thousands to millions Da. Typical applications of both polymers differ, therefore. PEG is used in pharmaceuticals, cosmetics, food, and as a laxative. It is soluble in water and various organic solvents. PEO is used due to its higher viscosity as a thickening agent, in lubrication, drug delivery, and water treatment. The use of both is well-established due to its versatile properties such as solubility in water, non-toxicity, and biocompatibility.

The key reasons for adding PEO/PEG to foods and drugs are:

Stabilizer and Thickener:

In foods PEO/PEG can help stabilize the texture of food products, preventing separation of ingredients (e.g., water

and oil). It acts as a thickening agent, improving the viscosity of liquids or semi-liquids, ensuring consistent mouthfeel and appearance.

In drugs PEO/PEG stabilizes the active ingredients in liquid formulations, ensuring uniform distribution and preventing the drug from settling or separating over time.

Moisture Retention and Humectant

In foods PEO/PEG can be used to retain moisture in food products, preventing them from drying out during storage. This is important in items like baked goods, candies, or processed meats, where moisture content is critical for texture and shelf life.

In drugs it can be used to prevent moisture loss in tablets or capsules, ensuring they don't become brittle or degrade during storage.

Solvent and Binder

In foods PEO/PEG is sometimes used to improve the solubility of food ingredients, allowing them to dissolve or blend more easily in liquid formulations. In drugs it acts as a binder in tablets and capsules, ensuring the ingredients stick together and maintain a stable form. PEG also aids in dissolving poorly soluble active pharmaceutical ingredients, enhancing drug absorption.

Laxative Effects

In drugs PEG is widely used in over-the-counter laxatives (e.g., Miralax). It works by drawing water into the colon, softening stools, and helping relieve constipation. Its osmotic properties make it an effective treatment for short-term bowel irregularities.

Lubricant

In drugs PEG is commonly used as a lubricant in the manufacturing of tablets and capsules, ensuring that the pills don't stick to machinery during production. It also makes swallowing easier for consumers by providing a smooth coating.

Plasticizer

In foods: In certain food coatings or films (e.g., for candies, some packaged goods), PEO/PEG helps make the material more flexible and less prone to cracking. In drugs: PEG can make drug coatings more flexible and durable, protecting the integrity of the active ingredients and ensuring proper release in the body.

Extended Shelf Life

In foods and drugs: PEG's stabilizing and moisture-retaining properties help extend the shelf life of products, keeping them fresh or effective for longer periods. It also

helps protect drugs from environmental factors like humidity, which can degrade active ingredients.

Inert and Safe Profile

PEO/PEG is considered to have a low toxicity profile and is generally recognized as safe by regulatory agencies like the FDA. This makes it an attractive choice for use in a wide variety of consumer products. It doesn't react with most active ingredients and remains chemically stable in different formulations. Common food products containing PEO/PEG are processed foods (candy, baked goods), beverages, ice cream, and various packaged items. PEO/PEG containing drugs are laxatives, ointments, creams, capsules, and tablet formulations. In summary, PEO/PEG is added to food and drug preparations for its stabilizing, moisture-retaining, and binding properties, as well as its versatility as a solvent and lubricant. Its safety, stability, and functionality make it widely useful across different industries. However, there are some potential risks associated with its use, particularly in food and drug preparations.

Examples of risks are:

Allergic Reactions and Sensitivity

In drug formulations, PEG can occasionally trigger immune responses or hypersensitivity reactions, including skin rashes or more severe anaphylactic reactions in susceptible individuals. Allergies to PEG in medications are generally uncommon.

Toxicity at High Doses: While PEO/PEG is generally considered non-toxic at low levels, when used in high doses, PEG can cause gastrointestinal distress, including nausea, vomiting, or diarrhea.

Contamination with Impurities: One concern is the potential contamination of PEO/PEG with harmful impurities during the manufacturing process. Ethylene oxide, a precursor to PEO, is a known carcinogen, and if residual ethylene oxide is present in PEO/PEG products, it could pose a health risk. Another contaminant of concern is 1,4-dioxane, which can form during PEG synthesis. 1,4-dioxane is classified as a probable human carcinogen, therefore regulations limit its presence in food and pharmaceuticals to very low levels.

Impact on Drug Bioavailability: In pharmaceuticals, PEG is used as a carrier or excipient to improve drug solubility and stability. However, in some cases, PEG can alter the pharmacokinetics of drugs. Prolonged use of PEGylated drugs may result in the accumulation of PEG in tissues, potentially impacting long-term safety.

PEGylation (the attachment of PEG chains to drugs): It reduces the body's immune response to some drugs, which might be beneficial for certain treatments, however, it may also decrease the efficacy of certain drugs by modifying their

absorption and clearance.

Environmental Concerns: PEG is not easily biodegradable. Its widespread use in consumer products has raised concerns about environmental persistence and potential ecological impacts, especially if it enters water supplies. Due to the extremely low concentration of the proposed systemic administration environmental concerns can be omitted.

Regulatory Status: Due to the concerns mentioned, regulatory agencies like the FDA and EFSA (European Food Safety Authority) generally consider PEG/PEO safe for use in pharmaceuticals and food products only within certain concentration limits. There are established guidelines to minimize the risks associated with contamination and toxicity.

Newly detected cancers

In the following the standard treatments for newly detected cancers will be discussed with concern of a possible and suitable combination with simultaneous DRP administration. The standard treatments of newly detected cancers depend on the type, stage, and location of the cancer, as well as the overall health of the patient. Typical treatments are surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, hormone therapy, and combinations of these methods.

Surgery

Surgery is often the first treatment for early detected cancers that are localized to a specific area. Surgery may involve tumor resection, part of an organ, or sometimes the entire organ, e.g., mastectomy for breast cancer, prostatectomy for prostate cancer. Surgery is most effective when the cancer has not yet metastasized. It is often combined with other treatments like radiotherapy and chemotherapy to reduce the risk of recurrence.

Radiation Therapy

Radiation therapy uses high-energy rays (like X-rays) to kill cancer cells or shrink tumors. The most common form is external beam radiation, where a machine directs radiation at the cancer. When applying internal radiation (Brachytherapy) radioactive materials are placed inside the body near the cancer site. It can be used as a primary treatment for some cancers (e.g., prostate cancer), before or after surgery to shrink or eliminate remaining cancer cells, or in conjunction with chemotherapy. A simultaneous systemic administration of DRP seems to be possible.

Chemotherapy

Chemotherapy uses drugs to kill rapidly dividing cancer cells throughout the body. Unlike surgery or radiation, which target specific areas, chemotherapy works systemically,

meaning it can treat cancer that has spread to other parts of the body. It is often used in combination with other treatments to enhance effectiveness. Sometimes, chemotherapy is given before surgery (neoadjuvant chemotherapy) to shrink tumors, or after surgery (adjuvant chemotherapy) to reduce recurrence. The side effects of chemotherapy are that it also affects normal cells, leading to nausea, hair loss, and fatigue. A simultaneous systemic administration of DRP seems to be possible.

Targeted therapies

Targeted therapies focus on specific molecular targets associated with cancer growth, such as proteins or genes involved in cancer cell survival and proliferation. These drugs are designed to attack cancer cells more specifically than chemotherapy, resulting in fewer side effects.

Examples are

Tyrosine kinase inhibitors, used for certain cancers like chronic myeloid leukemia and some lung cancers [36].

Monoclonal antibodies like trastuzumab (Herceptin), target specific cancer cell receptors [37].

Immunotherapy boosts or modifies the body's immune system to recognize and attack cancer cells. Typically, there are so-called checkpoint inhibitors that help the immune system recognize and attack cancer cells. They are used in cancers like melanoma and lung cancer. Immunotherapy can result in long-lasting remission, although not all cancers respond to this treatment.

CAR T-Cell Therapy is a newer form where a patient's T-cells are engineered to better attack cancer cells, e.g., for certain types of lymphoma and leukemia. ("*CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers*" was originally published by the National Cancer Institute NIH, 2022).

Hormone Therapy: Some cancers, such as breast and prostate cancers, are fueled by hormones like estrogen or testosterone. Hormone therapy works by blocking the body's hormone production or interfering with the hormone's action on cancer cells. Types are *Tamoxifen or Aromatase Inhibitors* for breast cancer, *Androgen Deprivation Therapy* (ADT) for prostate cancer. Hormone therapy is often used in combination with surgery, radiation, or chemotherapy to maximize effectiveness. *

Stem Cell or Bone Marrow Transplant is often used for blood cancers like leukemia and lymphoma. It involves replacing damaged bone marrow with healthy stem cells to help the body produce new blood cells after high doses of chemotherapy or radiation. In *Autologous Transplant*, the patient's own stem cells are harvested and returned. In *Allogeneic Transplant* stem cells come from a donor. ("*Stem*

Cell Transplants in Cancer Treatment" was originally published by the National Cancer Institute, 2023.

A simultaneous systemic administration of DRP seems in all cases to be possible.

Circulating and metastatic cancer cells

The question is whether CTC and metastatic cancer cells are identical from a structural and/or biological point of view. CTC and metastatic cancer cells share many similarities, but they are not identical in biological or structural terms. CTC have detached from the primary tumor and have the potential to seed new tumors in other parts of the body. CTC undergo changes that help them survive in the hostile environment of the blood. These changes might involve the acquisition of mesenchymal traits (via epithelial-mesenchymal transition, EMT) to increase motility and resist anoikis (cell death due to loss of attachment). Further CTC are highly heterogeneous, i. e., not all CTC have the ability to successfully establish metastatic colonies. Some CTC have stem cell-like properties, which increases their ability to initiate new tumors. CTC may retain characteristics of the primary tumor but may also express additional surface markers or structural changes that help them survive and evade immune detection in the blood. Metastatic cancer cells have successfully extravasated from the bloodstream and adapted to the microenvironment of the distant organ, which is often quite different from the original tumor site. Once metastatic cells invade a new tissue, they may further evolve, selecting traits that allow them to thrive in the new environment. They interact with the surrounding tissue to induce angiogenesis (new blood vessel formation), evade the immune system, and support their growth. Structurally, metastatic cells may differ *more* from primary tumor cells than CTC, having undergone genetic and phenotypic changes that allow them to colonize and grow in new environments. Summarizing the differences, CTC are transitory and mobile, found in circulation, while metastatic cancer cells have already colonized and are growing in a new tissue. CTC must adapt to survive in the bloodstream, whereas metastatic cells adapt to survive and grow in a specific tissue environment. Both types of cells exhibit significant heterogeneity, but metastatic cancer cells tend to undergo further adaptation and evolution once they establish in a distant organ, which may make them more distinct from the original primary tumor cells. Although both types originate from the primary tumor and they share key genetic mutations from the primary tumor, metastatic cells may accumulate more mutations over time.

Do CTC search locations in the circulation with favorable nutrition supply?

Although the process by which CTC spread and form metastasis is not yet fully understood, there is evidence that CTC prefer to settle down sites with favorable nutrient supply and oxygen levels. Important are

Microenvironmental Factors: Tissues, such as the liver, lungs, and bones, are common sites of metastasis because they provide a favorable environment in terms of nutrients, oxygen, and signaling molecules.

Chemotaxis and Homing: Cancer cells respond to certain signals or chemotactic gradients in the body, such as growth factors, cytokines, or hormones, which can guide them to specific organs or tissues. For example, breast cancer cells often metastasize to the bones because they respond to signals produced by bone cells and the bone microenvironment.

Seed and Soil Hypothesis: This concept, first proposed by Stephen Paget in 1889, suggests that metastasis depends on the interaction between the "seed" (cancer cells) and the "soil" (the microenvironment of a distant organ). Some environments are more favorable for the cancer cells to settle down and grow. Factors such as blood flow, nutrient supply, and local immune responses play a role in determining whether the cancer cells will successfully establish a new tumor.

Metabolic Preferences: Cancer cells often exhibit altered metabolism, favoring high glucose consumption and requiring a substantial energy supply (known as the Warburg effect). It is therefore more probable that they are attracted by areas with enhanced nutrient availability, such as highly vascularized regions of the body.

Vascular Niches: CTC may also lodge in specific vascular niches that provide a supportive environment for their growth. These niches often have enhanced blood supply and specific interactions with the cells lining the blood vessels (endothelial cells) that promote tumor survival.

In summary, while it's not known if cancer cells actively "search" for nutrient-rich locations, they do tend to settle in areas with conditions favorable for their growth, including nutrient supply, oxygen levels, and the other mentioned survival factors.

The assumption that CTC preferentially settle at sites with turbulent blood flow, where there may be enhanced nutrient supply, is still a hypothesis. While blood flow dynamics play a role in the metastasis process, several other factors also influence where CTCs settle and form secondary tumors. Key factors involved in CTC metastasis are:

Blood Flow and Shear Stress: Tumor cells experience varying shear stresses as they travel through the circulatory system. While some studies suggest that CTC may be more likely to extravasate (leave the bloodstream) in areas of disturbed or slow blood flow (such as capillaries or venules), turbulent flow itself is not necessarily a trigger for metastatic settlement. In fact, high shear stress in turbulent flow can damage or destroy tumor cells.

Vascular Structure: Metastasis often occurs in organs with highly vascularized tissue, like the lungs, liver, and bone marrow. These regions may have slower or more irregular blood flow, but nutrient supply is only one part of the equation. The microvascular environment, endothelial cell characteristics, and permeability of the blood vessels in these organs also play important roles in tumor cell settlement [38].

Endothelial Adhesion: CTC must interact with endothelial cells lining the blood vessels to extravasate. Specific molecular interactions (such as the expression of integrins and selectins) between CTC and the endothelium are critical for their ability to adhere to vessel walls and initiate metastasis. Areas of turbulent blood flow may not necessarily enhance these interactions [21].

Pre-metastatic Niche Formation: Metastatic sites are often "primed" by signals from the primary tumor, which can create a favorable microenvironment for CTC to settle. These signals may include secreted factors, extracellular vesicles, or changes in immune cell populations. Nutrient supply at these sites is a contributing factor, but it is not the only one [39].

Mechanical Trapping: CTC can also become mechanically trapped in small capillaries due to their size and reduced deformability, which explains why metastasis is common in organs with dense capillary networks, such as the lungs.

What is important in the context of the present publication is the fact that blood viscosity can change in cancer patients due to several factors related to both the disease and its treatments. These changes are influenced by the type of cancer, its progression, and specific physiological and biochemical changes. Here are some key factors:

Increased Blood Cell Counts (Hyperviscosity Syndrome): Certain blood cancers, like leukemia, lymphoma, and multiple myeloma, can lead to an increase in abnormal blood cells (like white blood cells or plasma cells) or proteins, raising blood viscosity. Multiple myeloma, in particular, can cause hyperviscosity due to excess immunoglobulin proteins in the blood [40].

Changes in Hematocrit Levels: Some cancers or their treatments may increase red blood cell counts, which raises hematocrit levels and thus viscosity. Conversely, anemia (often seen in cancer patients due to blood loss, poor nutrition, or treatment side effects) can lower hematocrit, decreasing blood viscosity [41].

Increased Inflammatory Proteins: Cancer and inflammation often go hand in hand, leading to elevated levels of proteins like fibrinogen. These proteins make blood thicker, contributing to higher viscosity.

Effects of Chemotherapy and Radiation Therapy: Treatments can alter blood cell counts and protein levels,

either increasing viscosity (due to higher inflammation) or decreasing it (due to anemia or blood loss).

Risk of Blood Clots: Higher blood viscosity in cancer patients can increase the risk of blood clots, particularly in cancers known to cause hypercoagulability (e.g., pancreatic cancer, lung cancer). This effect can contribute to complications like deep vein thrombosis or pulmonary embolism. Monitoring blood viscosity and clotting factors is therefore often part of managing cancer patients, particularly those at high risk for hyperviscosity syndrome or clotting complications.

Blood flow in liver or lungs

The hydrodynamics of blood flow in organs such as the liver and lungs is a key area of study in physiology, biomechanics, and bioengineering. Blood flow dynamics in these organs are highly specialized and essential to their function, both in delivering oxygen and nutrients and in removing waste products. Below is an overview of what is known about hydrodynamics in these two critical organs:

Blood Flow in the Liver (Hepatic Circulation):

The liver has a unique blood supply compared to other organs, characterized by the following features.

Dual Blood Supply: The liver receives blood from two major sources. The hepatic artery supplies oxygenated blood from the heart, accounting for 25% of the liver's blood flow. The portal vein provides nutrient-rich, deoxygenated blood from the gastrointestinal tract, accounting for about 75% of the liver's blood supply (https://www.nottingham.ac.uk/helmopen/rlos/biological-sciences/gastrointestinal-system/liver-anatomy/page_two.html).

Sinusoidal Blood Flow: The liver contains small capillary-like vessels known as sinusoids, which have quite different hydrodynamics compared to typical capillaries in other tissues. Sinusoids are wider, allowing slower, lower-pressure blood flow to maximize contact between the blood and hepatocytes (liver cells). The endothelium in the liver sinusoids is fenestrated, i. e., it contains pores, allowing for efficient exchange of materials between blood and liver cells [42].

Flow Dynamics: Blood flow in the liver is relatively slow and exhibits a complex, non-uniform pattern due to the arrangement of sinusoids. This allows for detoxification and metabolism, as well as nutrient storage and distribution. The liver's microvascular flow is influenced by local hemodynamic factors like pressure and shear stress, which can be modulated during liver diseases such as cirrhosis, where increased resistance to blood flow can lead to portal hypertension (<https://www.sciencedirect.com/topics/veterinary-science-and-veterinary-medicine/liver-sinusoid>).

Blood Flow in the Lungs (Pulmonary Circulation)

The lungs have a specialized circulatory system adapted for gas exchange. Blood from the right side of the heart is pumped into the pulmonary arteries, which carry deoxygenated blood to the lungs for oxygenation. Oxygenated blood is then returned to the left side of the heart via the pulmonary veins.

Low Pressure, High Flow: The pulmonary circulation operates at much lower pressures compared to systemic circulation. This is crucial because the lungs are delicate structures, and high pressure would damage the alveoli, the tiny air sacs where gas exchange occurs. Despite the lower pressure, the pulmonary circulation has a high flow rate due to the large volume of blood that must be oxygenated rapidly [43].

Alveolar-Capillary Interface: The alveoli are surrounded by a dense network of capillaries. The walls of these capillaries are extremely thin, allowing for efficient diffusion of gases (oxygen and carbon dioxide). Blood flow through these capillaries is optimized to match ventilation, i. e., airflow in the lungs, to ensure effective gas exchange. The matching of ventilation to perfusion is a critical aspect of lung physiology.

Regulation of Flow: The pulmonary circulation can constrict or dilate in response to oxygen levels. In areas of the lung with low oxygen (hypoxia), blood vessels constrict (hypoxic pulmonary vasoconstriction) to direct blood to better-ventilated areas. This mechanism maximizes gas exchange efficiency. Pulmonary blood flow also changes with body posture, exercise, and disease. For example, during exercise, pulmonary capillaries can recruit or distend to accommodate the increased cardiac output without a significant rise in pressure [44].

Key factors in the hydrodynamics of blood flow in both organs are **Vascular Resistance**: Both the liver and lungs regulate blood flow through the dilation and constriction of blood vessels in response to various signals (hormonal, chemical, mechanical).

Pressure Gradients: Blood flow in both organs is driven by pressure gradients. In the liver, the gradient is between the portal vein and hepatic veins, while in the lungs, it is between the pulmonary arteries and veins.

Shear Stress: In both the liver and lungs, shear stress (the force of blood flow against vessel walls) plays an important role in vascular health and function. Changes in shear stress can lead to endothelial cell responses that either protect or harm the vasculature depending on the context.

Pathological conditions in both organs:

Liver: In conditions like cirrhosis, fibrosis of liver tissue increases vascular resistance, leading to portal hypertension, which can disrupt the normal blood flow through the liver.

Lungs: In diseases like pulmonary hypertension, the pressure in the pulmonary arteries increases, leading to right heart strain and reduced oxygenation efficiency.

In summary, understanding the hydrodynamics of blood flow in the liver and lungs is critical for managing diseases affecting these organs, as abnormal blood flow is a hallmark of many serious conditions such as cirrhosis and pulmonary hypertension.

Preparation of injectable DRP doses

The preparation of injectable DRP doses suitable for cancer treatment consists for example in dissolving PEO of 4000 kDa molecular weight (Sigma-Aldrich, Union Carbide and others) in sterile saline to get a 0.1 % solution. To remove low molecular weight fractions, the solution has then to be dialyzed 24 h against saline by using a 50 kDa cutoff membrane. The PEO solution is finally diluted with saline to 50 ppm and sterilized before injection using a 0.22 µm filter [10,44]. Physiological saline solution (NaCl in a concentration of 0.15 mol/l) is almost identical to plasma. The injected PEO solution degrades mechanically within 2 or 3 days and the fragments are then excreted by the urinary system.

Concluding remarks

Metastatic cancer is responsible for approximately 90% of all cancer deaths. The proposed idea of using DRP in cancer treatment is still a novel and emerging concept, i.e., it has not yet become a standard approach in oncology. DRP have been primarily studied in the context of improving blood flow and reducing resistance in the cardiovascular system. Potential applications in cancer treatment include, for example, the enhancement of drug delivery and circulation. DRP have been studied for their ability to reduce the viscosity of blood and improve microcirculation. This could enhance the delivery of anticancer drugs to tumors, particularly in solid tumors that suffer from poor blood flow. Improved perfusion in tumor areas may allow more effective delivery of chemotherapeutic agents or nanoparticles used in cancer therapy. Tumors often create abnormal blood vessels that hinder effective drug penetration. By reducing blood flow resistance, DRP might be helpful. Another aspect where DRP could be useful is reducing hypoxia in tumors. Hypoxia is a major problem in many solid tumors, leading to resistance to therapies like radiation and chemotherapy. DRP could improve oxygen delivery by enhancing microvascular blood flow, reducing tumor hypoxia, and making tumors more susceptible to treatment. Further, poor circulation due to tumor burden or treatment side effects can complicate therapy. DRP might be used to improve overall blood circulation, thus reducing fatigue. This approach could potentially improve patients' overall condition, allowing

them to tolerate more aggressive therapies. Related fields of research are nanomedicine and drug carriers. DRP are widely used in nanomedicine as a component of polyethylene glycol (PEG)-modified nanoparticles and liposomes, which are used to deliver chemotherapy drugs. Further, vascular-targeted therapies to improve blood flow in tumors are ongoing, such as vascular normalization therapies and the use of nitric oxide donors. These strategies, which aim to improve the delivery of therapeutic agents, could potentially also be achieved by DRP. Although the systemic administration of blood soluble DRP in nanomolar concentrations may enhance blood flow and improve drug delivery in cancer treatment, the intravenous injection of DRP is not yet an established cancer treatment either for newly detected cancers or as cancer after care. Apart from further studies in specialized cancer research centers, case studies with small cohorts of patients could also be envisaged. Astonishingly, to the best of our knowledge the promising results of [10] have never been repeated or extended to other cancer types.

Developing commercially available injectable DRP solutions would require collaboration with companies that specialize in biomedical polymers, drug formulation, and injectable pharmaceutical delivery. Companies and organizations relevant for this type of development include:

Evonik Industries' healthcare division works with polymers used in drug delivery and provides custom polymer solutions and support for developing injectable formulations.

Croda International's life sciences division focuses on specialty excipients and drug delivery solutions, working with biocompatible and injectable-grade polymers.

Ashland Inc. specialized in pharmaceutical polymers, including injectable grades, and offers custom formulation services.

CSBio and Carbosynth produce specialty biochemicals, including polymers used in drug delivery and research applications. Further, a variety of models is available to study cancer biology, evaluate treatments, and develop new therapies, such as for instance.

Human Cancer Cell Lines derived from human tumors, examples are HeLa, MCF-7 (breast cancer), and A549 (lung cancer).

3D Cell Cultures simulate the tumor environment providing insight into cell-cell and cell-matrix interactions.

Animal Models:

Xenograft Models where human cancer cells are implanted into immunocompromised mice.

Genetically Engineered Mouse Models develop tumors spontaneously in specific organs.

Patient-Derived Xenografts where human tumor tissue is transplanted into mice.

Humanized Mouse Models with a humanized immune system allow to study immune response to cancer and immunotherapies. Even if the proposed systemic administration of DRP may not totally avoid metastasizing it can reasonably be considered that it would considerably decrease the number of metastasis deaths as leading cause of cancer mortality. To prove the concept the next steps in research should be the reproduction of the cited encouraging results and extending them to other cancer models in order to finally proceed to case studies.

References

1. Toms, B.A., First Int. Congr. Rheol. Some observations on the flow of linear polymer solutions through straight tubes at large Reynolds numbers (1948): 135–141,
2. Abdulbari, H.A., Chem. Ind. Chem. Eng. Q. Grafted natural polymer as new drag reducing agent: An experimental approach 18 (2012): 361–371,
3. Virk, P. S., Aiche J. Drag reduction fundamentals 21 (1975): 625–6564,
4. Kulicke, W.-M., Fließverhalten von Stoffen und Stoffgemischen (in German), Hüthig & Wepf, Basel/Heidelberg, New York (1986): 3-85738-115-4.
5. Sevic EM and Jain RK. Viscous resistance to blood flow in solid tumors: effect of hematocrit on intratumor blood viscosity, Cancer Res 49 (1989): 1989
6. Boron WF and Boulpaep EL, Medical physiology: a cellular and molecular approach, updated ed (2005): 1-4160-2328-3
7. Oertel jr H. Biostromungsmechanik (in German), Vieweg + Teubner, Wiesbaden (2008).
8. Pinkowski, A. and Lilienblum, W.: Technische Mechanik Can systemic administration of drag reducing agents reduce the risk of metastasizing after cancer surgery? – A hydrodynamics based hypothesis 35 (2015): 2015,
9. Pinkowski A and Lilienblum W. Horizons in Cancer Research HS Watanabe ed., Nova Science Publ., Inc., New York, ISBN (eBook): 9781-53618-284-2; ISSN: 2159-1326; chapter 5, Systemic Administration of Drag-Reducing Polymers to Combat Metastasis by Transforming Local Turbulence into Laminar Blood Flow
10. Ding Z, Joy M, Kameneva MV and Roy P. Breast Cancer – Targets and Therapy Nanomolar concentration of blood-soluble drag-reducing polymer inhibits experimental metastasis of human breast cancer cells 61 (2017): 61,
11. Kameneva MV, Bragin D, Nemoto E and Simmons R Hemorheologic approach for reduction/prevention of cancer metastasis formation, US Patent (2020).
12. Raffaghello L, Lee Ch, Safdie FM, Wei M, Madia F, Bianchi G et al PNAS. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy 105 (2008): 8215.
13. Bark DL, Vital E, Oury C, Lam WA, Gardiner EE, Communication from the ISTH SSC Subcommittee on Biorheology, Journal of Thrombosis and Haemostasis (2024).
14. Lilienblum W and Pinkowski A. Global Journal of Medical Research (ISSN 9755853). Hydrodynamics based Proposal to Substitute Heparin by Drag Reducing Polymers 17 (2017): 2017
15. Zhang L, Fan M, Napolitano F, Gao X, Xu Y & Li L. Journal of Translational Medicine. Transcriptomic analysis identifies organ-specific metastasis genes and pathways across different primary sites 19 (2021): 1-11.
16. Tang, Tianyu, et al. Signal transduction and targeted therapy 6 (2021): 72. Advantages of targeting the tumor immune microenvironment over blocking immune checkpoint in cancer immunotherapy.
17. Albini, Adriana, et al., Nature reviews Clinical oncology 9 (2012) 498. Cancer prevention by targeting angiogenesis.
18. Esteva, Francisco J, et al. The lancet oncology. Immunotherapy and targeted therapy combinations in metastatic breast cancer 20.3 (2019): e175-e186
19. Dawson NA. www.uptodate.com ©. UpToDate, Inc. and/or its affiliates, Official Reprint; Patient education: Treatment for advanced prostate cancer (Beyond the Basics) 2024.
20. Kulkarni VS, Alagarsamy V, Solomon VR, Jose PA and Murugesan S, Russ J. Bioorg. Chem. Drug Repurposing: An Effective Tool in Modern Drug Discovery 49 (2023): 157.
21. Krog BL and Henry MD. Adv Exp Med Biol. Biomechanics of the Circulating Tumor Cell Microenvironment 1092 (2018): 209–233.
22. Joyner MJ and Casey DP. Physiol Rev. Regulation of Increased Blood Flow (Hyperemia) to Muscles During Exercise: A Hierarchy of Competing Physiological Needs 95 (2015): 549–601
23. Toyokawa G, Seto T, Takenoyama M and Ichinose Y. Cancer Metastasis Rev. Insights into brain metastasis in patients with ALK+ lung cancer: is the brain truly a sanctuary? 34 (2015): 797-805

24. Banfalvi, G., Cancer Metastasis Rev. Metastatic view of breast cancer 31 (2012): 815-22
25. Neuzillet C, Hammel P, Tijeras-Raballand A, Couvelard A and Raymond E. Cancer Metastasis Rev. Targeting the Ras-ERK pathway in pancreatic adenocarcinoma 32 (2013): 147-62
26. Gunasinghe D, Wells A, Thompson Erk W and Hugo Honor J. Cancer Metastasis Rev. Mesenchymal-epithelial transition (MET) as a mechanism for metastatic colonisation in breast cancer 31 (2012): 469-78
27. Bidard F-C, Fehm T, Ignatiadis M, Smerage JB, Alix-Panabières C, et al Cancer Metastasis Rev. Clinical application of circulating tumor cells in breast cancer: overview of the current interventional trials 32 (2012): 179–188.
28. Louedec FL, Leenhardt F, Marin C, Chatelut E, Evrad A, and Ciccolini J., Vaccines (Basel). Cancer Immunotherapy Dosing: A Pharmacokinetic/Pharmacodynamic Perspective 31 (2020): 632
29. Lanier OL, Pérez-Herrero E, D'Andrea AP, Bahrami K, Lee E, et al. iScience. Immunotherapy approaches for hematological cancers 25 (2022): 105326
30. Seker-Polat F, Degirmenci NP, Solaroglu I and Bacci-Onder T. Cancers (Basel). Tumor Cell Infiltration into the Brain in Glioblastoma: From Mechanisms to Clinical Perspectives 14 (2022): 443.
31. Pinter M, Trauner M, Peck-Radosavljevic M and Sieghart W ESMO Open. Cancer and liver cirrhosis: implications on prognosis and management 1 (2016): e000042
32. Morrison J, Haldar K, Kehoe S and Lawrie TA. Cochrane Database Syst Rev. Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer (2012): CD005343.
33. Yousem DM, Gad K and Tufano RP. AJNR Am J Neuroradiol. Resectability Issues with Head and Neck Cancer 27 (2006): 2024–2036.
34. Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA and Hamilton, SM Ann Surg. Gastric Adenocarcinoma-Review and Considerations for Future Directions 241 (2005): 27–39.
35. Hayes AJ, Nixon I, Strauss DC, Seddon BM, Desai A, Benson Ch, Judson IR and Dangoor A. British Journal of Cancer UK guidelines for the management of soft tissue sarcomas (2024).
36. Pottier Ch, Fresnais M, Gilon M, Jérusalem G, Longuespée R, and Sounni NE. Cancers (Basel) Tyrosine Kinase Inhibitors in Cancer: Breakthrough and Challenges of Targeted Therapy 12 (2020): 731.
37. Gemette JJ and Mukheri SK. AJNR Am J Neuroradiol. Trastuzumab (Herceptin) 32 (2011): 1373–1374.
38. Rajput S, Sharma PK, Malviya R, Medicine in Drug Discovery Fluid mechanics in circulating tumour cells: Role in metastasis and treatment strategies (2023): 100158.
39. Wang Y, Jia J, Wang F. et al., Sig Transduct Target Ther. Pre-metastatic niche: formation, characteristics and therapeutic implication 9 (2024): 236.
40. Musick JO, Fibben KS and Lam WA Curr Opin Hematol. Hyperviscosity syndromes; hemorheology for physicians and the use of microfluidic devices 29 (2022): 290–296.
41. Zimmerman R. et al. Anesth Analg. Posttransfusion Increase of Hematocrit per se Does Not Improve Circulatory Oxygen Delivery due to Increased Blood Viscosity 124 (2017): 1547-1554.
42. Tweedy HT, Bonfiglio A, Leungchavaphongse K, Repetto R. IFMBE proceedings Mathematical Modeling of Blood Circulation in the Liver 31 June (2010).
43. West JB. Am J Physiol Regul Integr Comp Physiol. Comparative physiology of the pulmonary blood-gas barrier: the unique avian solution 297 (2009): R1625–R1634.
44. Kimberley JD-S et al. Chest. Epub 2016 Sep 16; Hypoxic Pulmonary Vasoconstriction: From Molecular Mechanisms to Medicine 151 (2017): 181-192
45. Bowen D and Joong Sup Shim, Molecules Targeting Epithelial–Mesenchymal Transition (EMT) to Overcome Drug Resistance in Cancer 21: 965,
46. Gu Y, Yu S, Mou J, Wu D and Zheng S. Materials. Research Progress on the Collaborative Drag Reduction Effect of Polymers and Surfactants 13 (2020): 444.
47. Pinkowski A and Lilienblum W. preprint posted. A Hydrodynamic Approach to Cancer (2015).