Nanomedicines-based intraperitoneal therapy for the treatment of peritoneal carcinomatosis – mission possible?

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Abstract

Intraperitoneal (IP) drug delivery represents an attractive strategy for the local treatment of peritoneal carcinomatosis (PC). Over the past decade, a lot of effort has been put both in the academia and clinic in developing IP therapeutic approaches that maximize local efficacy while limiting systemic side effects. Also nanomedicines are under investigation for the treatment of tumors confined to the peritoneal cavity, due to their potential to increase the peritoneal retention and to target drugs to the tumor sites as compared to free drugs. Despite the progress reported by multiple clinical studies, there are no FDA approved drugs or formulations for specific use in the IP cavity yet. This review discusses the current clinical management of PC, as well as recent advances in nanomedicines-based IP delivery. We address important challenges to be overcome towards designing optimal nanocarriers for IP therapy *in vivo*.

Abbreviations

CRS   Cytoreductive Surgery

HA   Hyaluronic Acid

IP   Intraperitoneal

IPEC   Intraperitoneal Chemotherapy

HIPEC   Hyperthermic IntraPeritoneal Chemoperfusion

IFP   Interstitial Fluid Pressure

MDR   Multi Drug Resistance

Microparticles   MPs

Nanoparticles   NPs

Paclitaxel   PTX

PC   Peritoneal Carcinomatosis

PIPAC   Pressurized IntraPeritoneal Aerosol Chemotherapy

VEGF   Vascular Endothelial Growth Factor

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1. Introduction

Primary cancer occurring in organs confined to the peritoneal cavity (e.g. ovary, liver, colon, and pancreas) might lead to the migration of cancer cells to the peritoneal cavity. Attachment of free-flowing cancer cells to the mesothelial layer of the peritoneal membrane results in the formation of peritoneal carcinomatosis (PC). In the USA alone, there are about 250,000 cases of cancer originating from organs in the peritoneal cavity (e.g., ovarian, pancreatic, colorectal, gastric and liver)[1]. Unfortunately, most primary tumor sites do not cause clear clinical symptoms that enable the early detection of the peritoneal spread of cancer cells. The detection of PC thus mostly occurs at a later disease stage when a large amount of tumor nodules is already distributed over the peritoneal surfaces. The presence of these multiple peritoneal metastases confers a poor prognosis [2].

Selected patients with PC benefit from surgical cytoreduction, aiming to remove all visible peritoneal metastases. Depending on the histology and grade of the disease, either perioperative or postoperative intravenous (IV) chemotherapy can be administered. Despite macroscopically complete cytoreductive surgery (CRS), many patients develop recurrent PC [3]. Hence, active adjuvant treatments are needed to remove persisting minimal residual disease and improve the survival of patients diagnosed with PC. The past decade has witnessed a significant progress in developing IP adjuvant techniques. Most newly developed techniques focus on the local administration of chemotherapeutics. The rationale for IP therapy is the ability to achieve a high locoregional (peritoneal) drug concentration, while avoiding systemic toxicity [4]. Conventional chemotherapeutics might, however, rapidly leak from the peritoneal cavity and display little specificity towards cancer cells. Therefore, the use of nanomedicines to prolong the residence time in the peritoneal cavity and to specifically target tumor cells is being explored. In this review we aim to discuss the progress, barriers and challenges in employing nanomedicines for IP therapy of PC, with a special focus on strategies that are employed to increase the residence time of nanomedicines in the peritoneal cavity. To do so, we first focus on the main techniques that are currently used in the clinical management of

PC using local administration of conventional chemotherapeutics. We also address the challenges and hurdles in tailoring nanomedicines for IP delivery *in vivo*, including biodistribution and tumor penetration. Finally, we discuss ongoing clinical trials with nanomedicines for PC therapy and reflect on possible strategies to overcome current limitations upon administration of nanomedicines.

2. Anatomy and role of the peritoneal membrane

The peritoneal membrane covers the visceral, abdominal and pelvic organs and has a total surface of 1.5 m² on average [5]. It is composed of several layers of connective tissue as demonstrated by Baron et al. [6]. The first layer is comprised of mesothelial cells interconnected by tight junctions, which secrete surface hyaluronan as depicted in Figure 1A. The mesothelial layer functions as a barrier that protects from physical damage and surface adhesion [7]. A submesothelial basement membrane separates the mesothelial layer from the interstitial space, which contains fibroblasts, collagen and other molecules as a first "defense line" against macromolecules (Figure 1A). The last layer consists of negatively charged endothelial cells – a second "defense line" that prevents the passage of large macromolecules into the peritoneal cavity (Figure 1A).

Under normal conditions (Figure 1A), the oncotic pressure that is exerted by plasma proteins (mainly albumin) across the peritoneal membrane (between the endothelial layer and the mesothelial layer) restricts the diffusion of water into the abdominal cavity due to the reabsorption of water that occurs into the capillaries from the interstitial space [8]. In the majority of the PC cases, however, this homeostasis is disrupted by an increased microvascular permeability which is believed to be mainly induced by the vascular endothelial growth factor (VEGF) [9, 10]. Together with the secretion of cytokines and chemokines in the surrounding of the peritoneum, the structure of the membrane is altered leading eventually to a net change in the flow direction of the fluid (i.e. oncotic pressure) into the peritoneal cavity and consequently, to the formation of an albumin-rich ascites fluid in the peritoneal cavity (Figure 1B). The exact mechanism by which the ascites fluid accumulates in the abdomen is very complex, and not fully elucidated yet. It is hypothesized that different factors play an

important role in the formation of the ascites fluid, such as lymphatic obstruction and osmotic water transport following the leakage of proteins from microcapillaries into the peritoneal cavity [11].
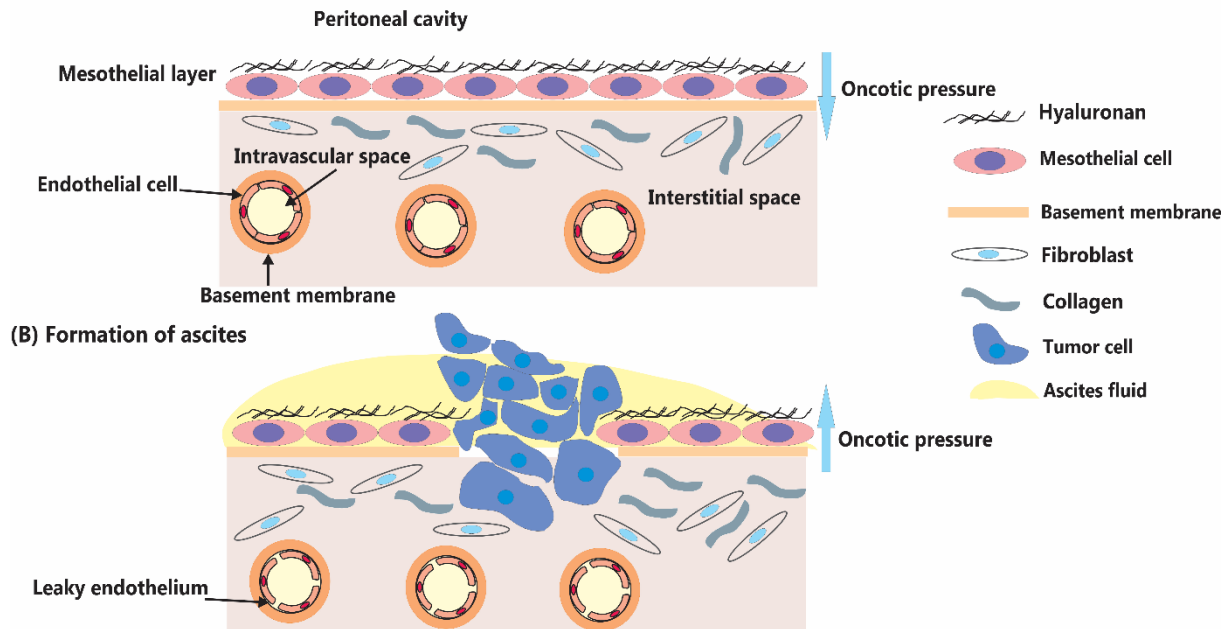
Figure 1. The peritoneal membrane and formation of ascites fluid. (A) Structure of the peritoneal membrane under normal conditions and **(B)** disruption of the peritoneal membrane in peritoneal carcinomatosis, leading to the formation of ascites.

Interestingly, it has been shown that the peritoneal membrane does not correspond to the classic semi-permeable model, but rather is highly permeable to both water, small solutes and proteins [7]. In fact, the peritoneal membrane does not represent a substantial physical barrier for IP administered low-molecular weight drugs, indicating that small chemotherapeutics can easily redistribute to the systemic circulation [7, 12, 13]. There is no consensus, however, as to which extent the peritoneal membrane poses a barrier to nano-or micrometer sized particles. Also, it is not known if the permeability of the peritoneal membrane changes in function of peritoneal disease progression due to the infiltration of tumor cells in the mesothelial cell layer and disruption of the basement membrane.

3. Local chemotherapy for the treatment of peritoneal carcinomatosis

3.1. Rationale behind using IP therapy

IP therapy aimed at targeting tumors within the peritoneal cavity offers pharmacokinetic advantages when compared to systemic (IV) administration of chemotherapeutics. As postulated by Dedrick *et al.*, higher concentrations of drug are expected to reach peritoneal tumors following IP delivery compared with the systemic delivery [14, 15]. Also, IP delivery increases the concentration of drug in the vicinity of hypoxic, small peritoneal metastases (less than 1 mm in diameter), which lack an established vasculature and are therefore difficult to treat using IV administration [16]. Finally, similar to any other regional cancer therapy, administration of drugs directly into the site of action lowers systemic toxic effects [17]. It should be noted that none of the available chemotherapeutics has been specifically approved for IP administration. Therefore, IP chemotherapy is currently used off label with agents developed for IV administration such as Doxorubicin [18], Fluorouracil analogues [19], Paclitaxel (PTX) [20], and Platinum-based compounds [21].

3.2. Current clinical management of PC

Nowadays, the most common IP delivery technique in many clinical centers is repeated IP instillation of chemotherapeutics using a port catheter after cytoreductive surgery (CRS) [22, 23]. During CRS, all macroscopic disease is removed by a combination of organ resections and peritonectomy procedures. The IP cycles are usually initiated 1-3 weeks after surgical debulking, and the catheter is removed after the last cycle of IP chemotherapy is completed. Another option for IP delivery of chemotherapeutics involves intraoperative continuous chemoperfusion (IPEC), immediately after CRS. Intraperitoneal chemoperfusion is usually performed under hyperthermic conditions (41.5°C), known as HIPEC [24] (Figure 2). It is assumed that HIPEC leads to a homogenous distribution of the administered drug throughout the abdominal cavity and enhances penetration of the drug into the remaining solid tumor nodules [25, 26]. During the combined procedure, the peritoneal cavity is perfused during 30-120 min with chemotherapy using a closed or semi-open perfusion circuit consisting of inflow and outflow drains, a roller pump, reservoir, and heating element. In the largest single-center study, between the

years 1991 till 2013, 1,000 patients with PC underwent CRS followed by HIPEC [27]. The authors showed a significant improvement in the survival rate and a substantial decrease in complications, stoma creation and transfusion requirement over time. It should be noted that surgery combined with HIPEC is invasive and time consuming. Also, standardized treatment protocols regarding drug schedule and dose, perfusion temperature, and perfusion duration are currently unavailable [28].
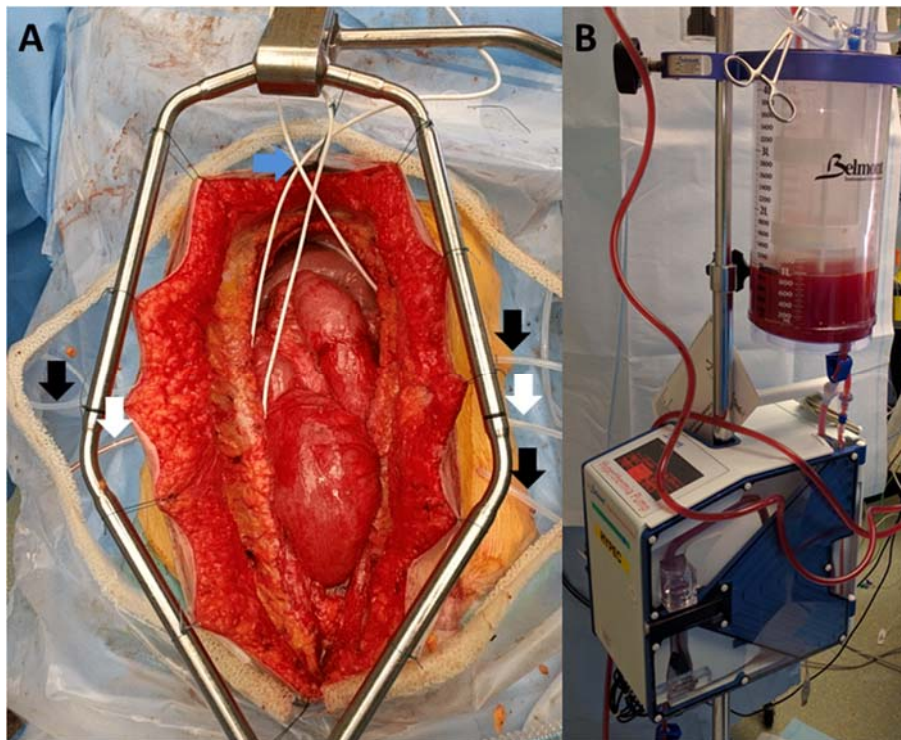
Figure 2. Surgical procedure of HIPEC. (A) View of the open abdomen after cytoreductive surgery for peritoneal carcinomatosis. Then, hyperthermic intraperitoneal chemotherapy (HIPEC) is performed through inflow (white arrows) and outflow (black arrows) tubes that are inserted in the abdominal cavity and connected with a pump, which installs an ongoing circulation. Temperature is continuously measured using three probes (blue arrow) placed in the abdominal cavity. **(B)** A roller pump establishes a continuous circulation of chemotherapy in and out the abdominal cavity.

A very recent new method of intraperitoneal cytotoxic drug delivery for the treatment of PC is Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) [29], which is performed during

laparoscopy. After creation of a standard CO_2 pneumoperitoneum (working pressure 12-15 mm Hg), several balloon trocars are introduced into the abdominal cavity. A disposable nebulizer or micropump (MIP®, Reger Medizintechnik, Rottweil, Germany) is positioned into the abdomen through one of the trocars and connected with a high pressure injector through a dedicated high-pressure line. The cytotoxic solution (Figure 3B) is injected under a pressure of 20 bar, and the resulting aerosol dispersed in the abdomen (Figure 3C). After complete administration, a generator (Ultravision, Alesi Surgical Ltd., UK) is activated, inducing electrostatic precipitation of the airborne particles on the peritoneal surface (i.e., electrostatic PIPAC or E-PIPAC). This pressurized state at 12 mmHg is maintained for 30 minutes. Thereafter, the capnoperitoneum is deflated through a closed suction system.

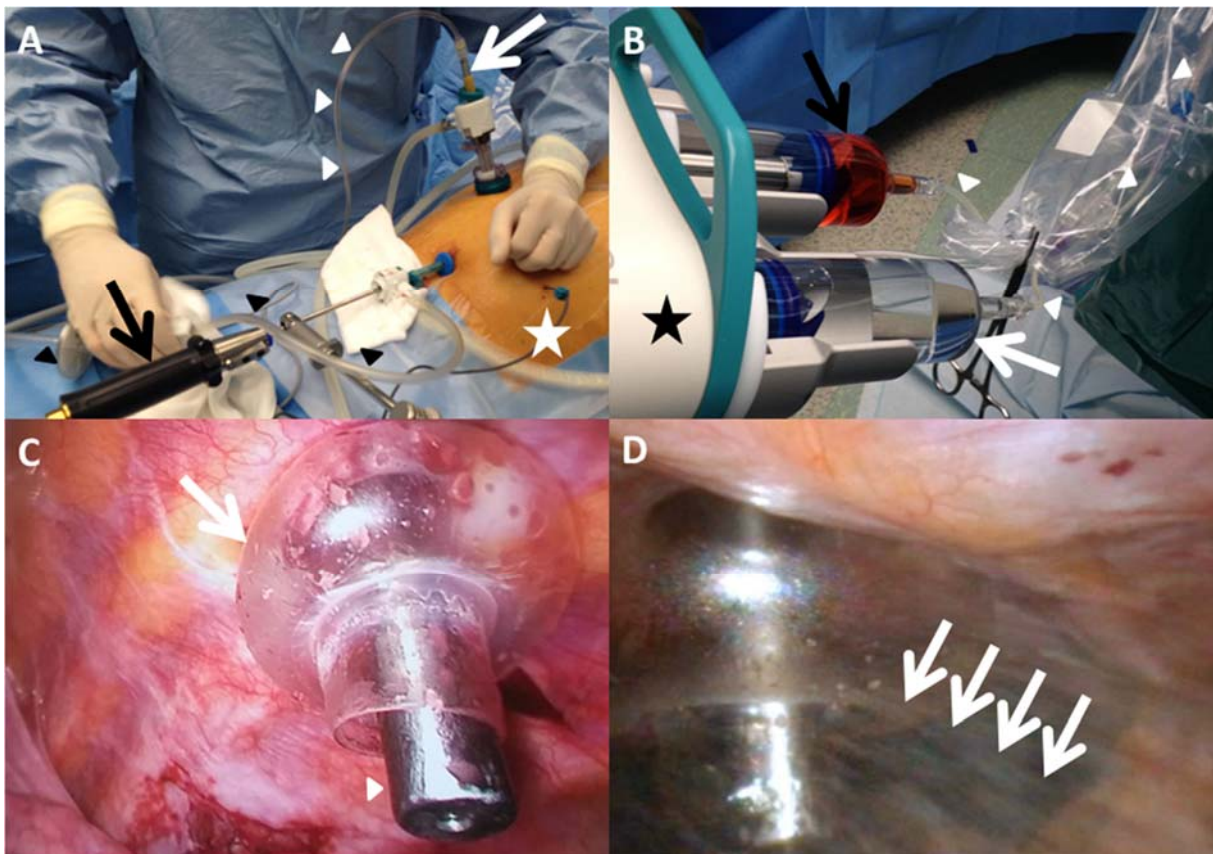**Figure 3. Surgical procedure of E-PIPAC**. **(A)** A capnoperitoneum is established during laparoscopy. A nebulizer (white arrow) placed in a 10 mm balloon trocar is connected with a high-pressure line (white arrowheads). A 5 mm camera (black arrow) is inserted in a 5 mm balloon trocar to inspect the nebulization in the abdomen. Once all the cytotoxic agents are injected, electrostatic precipitation of

aerosol on the peritoneum is induced through a dedicated catheter (star) connected with a generator. After E-PIPAC, the abdomen is deflated through a closed aerosol waste system with filter (black arrowheads). **(B)** Double head injector (star) with 2 syringes for doxorubicin (black arrow) and cisplatin (white arrow) administration. Both syringes are connected with a high-pressure line (white arrowheads). **(C)** Intra-abdominal view of the tip of the nebulizer (white arrowhead) inserted in the 10 mm balloon trocar (white arrow) before initiation of E-PIPAC. **(D)** Intra-abdominal movement of airborne cytotoxic particles (multiple arrows) during injection.

The working mechanism of PIPAC is based on local administration of cytotoxic agents on the tumoral surface in the abdominal cavity. The aerosol form accomplishes homogeneous drug distribution [30], while it is believed that the high intra-abdominal pressure enhances tissue penetration and antitumor effects [31, 32]. As a consequence, a low dose of chemotherapy can be used, causing low systemic drug uptake and toxicity [29, 33]. Interestingly, Solass and coworkers indeed showed that clinical PIPAC therapy with Doxorubicin achieves high tissue drug concentrations, even though a relatively low dose is nebulized [29].

Other possible advantages include minimal patient discomfort, the repeatability of the procedure, global quality of life improvement, and the possibility to combine PIPAC with systemic chemotherapy [34, 35]. Experimental and clinical studies show that PIPAC has promising antitumor activity in ovarian, gastric, and colorectal carcinomatosis [36, 37]. Prospective studies (NCT02604784, NCT02320448, NCT01854255), investigating the efficacy of PIPAC in recurrent gastric cancer are currently recruiting patients. A phase 1 dose-escalation trial has been initiated recently in recurrent ovarian cancer (NCT02475772). It is clear, however, that PIPAC is still in its infancy and further clinical research is needed.

4. Future directions in PC therapy

A major drawback of currently used local therapies for PC is the significant risk of recurrent peritoneal disease [38, 39]. Due to the short exposure time to conventional small chemotherapeutics, which rapidly leak from the peritoneal cavity, there is a need for therapeutic approaches that enable a prolonged residence time of chemotherapeutics in the peritoneal cavity following CRS. One such approach that is investigated, is the use of nanoparticles that carry and deliver chemotherapeutics specifically into tumors.

4.1. Rationale for using nanomedicines for IP therapy

Nanoparticles (NPs) are particles with a size that ranges from 1 to 1000 nanometer (nm) in diameter. Due to their size, versatility and the ability to easily modify their surface, NPs are excellent candidates to cross biological barriers and deliver different therapeutics into cells. Also, NPs can potentially slow down systemic absorption, decrease systemic toxicity [40] and extend the exposure time of the drugs to peritoneal tumors. Furthermore, NPs can be functionalized to selectively accumulate at tumor sites [41, 42]. NPs that are used as vehicles for the delivery of drugs and biopharmaceuticals are known as "nanomedicines".

Generally speaking, NPs are roughly divided into two main types: (1) lipid-based NPs and (2) polymer-based NPs. The most used lipid-based nanomedicines for biomedical applications are liposomes [43], while Poly (lactic-co-glycolic acid) (PLGA) is one of the most successfully developed polymers used in drug delivery [44]. The choice of NPs for a specific application mostly depends on the physico-chemical properties of the desired cargo (e.g. hydrophilicity/hydrophobicity, charge, solubility, etc.) and the route of administration, as well as on the extracellular and intracellular barriers it is expected to cross in order to successfully reach the site of action. To date, there are some nanomedicines approved for clinical use and several more in clinical trials [45]. Nanomedicines have also played a vital role in cancer therapy [41, 42], with a total of 12 clinically approved nanomedicines for anti-cancer therapies [46]. None of these nanomedicines, however, are intended for IP cancer therapy.

Numerous attempts have been made to deliver chemotherapeutics into tumors confined to the peritoneal cavity using NPs (Figure 4A), via both IV and IP routes [47-49]. We have also recently reviewed different non-viral nucleic acid delivery systems that were IP administered for the treatment of peritoneal cancer [50]. In the current review, we do not aim to overview the different types of nanoparticle systems and their building blocks as such, but to focus on general *in vitro* and *in vivo* aspects related to IP delivery of nanomedicines that are currently still often overlooked.

4.2. *In vitro* stability and biological activity of NPs in the presence of ascites fluid

Generally speaking, *in vitro* optimization of nanomedicines is required as a first development step, and this includes basic characterization of the size and surface charge, followed by toxicity, uptake, and biological activity assays in the relevant cell type. Nevertheless, *in vitro* optimization is often carried out in biofluids that do not resemble the *in vivo* situation, and the impact of the relevant biofluids that nanomedicines will encounter upon *in vivo* administration is often not investigated. It is becoming increasingly clear that NPs present in biofluids (e.g. blood, plasma, serum, saliva, peritoneal fluid, etc.) interact with different components including proteins and degrading enzymes that may lead to their aggregation, premature release of cargo, loss of targeting capabilities, decrease of cellular uptake, and eventually dramatic limitation of biological activity [51-56]. In this context, we have recently established an *in vitro* model to evaluate the performance of NPs in the presence of ascites fluid obtained from a patient diagnosed with peritoneal carcinomatosis. By using advanced microscopy techniques, we were able to determine the aggregation and disintegration of NPs in the undiluted ascites fluid, as parameters to follow their colloidal stability in function of time [57]. Our data demonstrate that the ascites fluid does not only influence the colloidal stability of the NPs, but also drastically lowers cellular uptake of liposome-siRNA complexes. Thus, even NPs such as PEGylated liposomes that were colloidally stable in ascites fluid (in terms of aggregation and release), lost their ability to silence genes in SKOV-3 human ovarian cancer cells due to their incapability to carry the siRNA into the cells [51]. It should be noted that generally, only limited amount of ascites fluid has developed in the patients which are eligible for CRS and adjuvant IP therapy. Before the development

of ascites, only a small amount of IP fluid is present, which cannot be extracted from patients to optimize *in vitro* performance of NPs. Whether or not the small amount of IP fluid limits the therapeutic potential of *in vivo* administered nanoparticles to the same extent as ascites fluid remains to be elucidated. Nevertheless, we do recommend to optimize the *in vitro* behavior of NPs in ascites fluid, before moving on to the *in vivo* evaluation of NPs.

4.3. *In vivo* barriers and challenges upon IP administration of NPs

4.3.1. Biodistribution of NPs following IP injection

Apart from colloidal stability, an important feature in anti-tumor activity of nanomedicines is their fate following administration. Ideally, nanomedicines should circulate, extravasate (in case of IV injection), accumulate and finally penetrate into the tumor. Unlike for IV administration, where tens of studies investigated the biodistribution and ability of different nanomedicines to accumulate at tumor sites [58, 59], only (very) limited data are available on the biodistribution of NPs following IP injection (table 1). The biodistribution of non-PEGylated (450 nm in size) and PEGylated (30-100 nm in size) graphene oxide NPs was assessed in healthy animals following IP administration [60]. Aggregated and immobile NPs were found in the abdomen for the non-PEGylated formulation, whereas the mobile PEGylated formulations accumulated mainly in the liver and spleen. Langer and coworkers evaluated 265 nm PLGA NPs of 90 kDa as strategy to prolong drug delivery in the murine peritoneum and compared the biodistribution with 5-250 µm sized PLGA microparticles (MPs) [61]. All NPs were cleared from the peritoneum within 2 days after administration, and accumulated in the mononuclear phagocyte system (MPS) organs, namely the liver and spleen. MPs were retained in the peritoneal cavity for a longer time period, but a high incidence of adhesions 2 weeks after injection of the MPs made them unsuitable for long term delivery to the peritoneum [61]. Similarly, Tsai et al. examined the effect of carrier size on the disposition and anti-tumor activity of paclitaxel (PTX) [62]. In particular, PTX loaded gelatin MPs and NPs, as well as Cremophor micelles were systematically studied in mice bearing Hs766T pancreatic human cancer cells. Again, NPs were more rapidly cleared from the peritoneal

cavity, with less than 0.1% remaining in peritoneal lavage samples 24 h following IP administration. MPs exhibited the slowest clearance and the longest residence time in the abdominal cavity, which was correlated with a ~2 fold increase in the survival time when compared to the NPs and Cremophor micelles. The authors attributed this clearance profile to the dimensions they found for the lymphatic duct openings (known as stomata) on the diaphragm of mice, which ranged on average from 0.7 to 15.5 μm in length and 0.5 to 8.2 μm in width. Therefore, NPs smaller than these openings were rapidly cleared into the systemic circulation, while a more slow absorption occurred for MPs which were similar in size to the openings [62]. Also, Hirano and Hunt investigated the size effect on the peritoneal retention of liposomes of 48, 170, 460 and 720 nm in rats [63]. They observed no size effect in this range, as all liposomes remained below the estimated size limits that would restrict their entrance into the lymphatic capillaries. When Sadzuka et al. investigated the size effect for negatively charged liposomes of 155, 605 and 4225 nm, they came to comparable conclusions [64]. Again, no significant difference in clearance was observed for the small and medium sized vesicles, while the larger liposomes indeed were retained for a longer time in the peritoneal cavity 8 and 24 hours after injection. When neutral liposomes were used, Mirahmadi concluded that 1000 nm sized particles were the most optimal to achieve high peritoneal retention [65]. Dadashzadeh et al., however, looked into the effect of size, charge, lipid composition and PEG coating on peritoneal retention in healthy female NMRI mice using 100 nm and 1000 nm radiolabeled liposomes [66]. The charge of the liposomes seemed to be the most important factor that determined the retention in the abdominal cavity, with cationic liposomes being longer retained than negatively charged liposomes. The effect of size on peritoneal clearance was dependent on the charge of the liposomes. 100 and 1000 nm negatively charged liposomes were equally rapidly cleared, most likely through macrophage uptake. Size did matter for the cationic liposomes, where the 1000 nm cationic liposomes had the highest retention in the peritoneal cavity, with up to 25% of the initial dose still remaining 48 hours following administration. For 100 nm cationic liposomes, 20% of the injected dose could still be retrieved after 24 hours. In the first hours following injection, PEGylation of the cationic liposomes even further increased the

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peritoneal retention, presumably because of interference with the uptake of PEGylated liposomes in the macrophages. The authors concluded, overall, that the 100 nm cationic liposomes are the most suitable for IP drug delivery due to uniform distribution in the peritoneal cavity and resistance to uptake by peritoneal macrophages. It should be noted that the authors did not determine the actual size of liposomes after injection into the abdomen. As we previously demonstrated that especially cationic liposomes are sensitive to aggregation, we speculate that the high retention of the 100 nm cationic liposomes observed by Dadashzadeh et al. could potentially be attributed to aggregation of the cationic liposomes in the peritoneal cavity to micrometer sized aggregates [57], which no longer efficiently cross the lymphatic openings. Also, it is of importance to mention that the vast majority of the above mentioned biodistribution studies were performed in healthy animals (see table 1). Therefore, at the moment it is not clear whether or not the residence time of particles in the peritoneal cavity would be changed in the presence of PC, for example by changing the barrier function of the peritoneum, by altering the amount and activity of macrophages present in the peritoneal cavity or by changes in the content and composition of proteins in the peritoneal fluids, which might bind and alter the biological activity of NPs as mentioned under section 4.2.

In general, two major mechanisms for drug clearance from the peritoneal cavity to the systemic circulation are suggested: (1) direct absorption through the peritoneum and (2) drainage via the lymphatic ducts. For small molecules with a molecular weight of less than 20 kDa, absorption through the peritoneum is the major pathway, as shown by Flessner and co-workers [12]. For larger compounds such as NPs and MPs, the studies above demonstrate that lymphatic drainage represents the major clearance pathway [63, 67]. The lymphatic drainage and rapid clearance of colloidally stable NPs (that are diffusing and do not form aggregates) from the peritoneal cavity seems inevitable, in such a way that NPs are cleared within several hours (depending on the size) following administration, resulting in a low residence time in the abdomen. Nevertheless, it should be noted that NPs that are larger than 500 nm in size tend to stay in the lymph nodes, while smaller NPs pass through the lymph nodes and end up in the systemic circulation [63]. This lymphatic targeting of NPs has long time ago already been

proposed by Maincent et al. [68] as a promising strategy to treat tumors that make use of the lymphatic pathways to spread and metastasize in the peritoneal cavity.

Table 1. Biodistribution of NPs following IP administration

Formulation	Hydrodynamic diameter & surface charge (if available)	animal model	Outcome	Reference
PEGylated and non-PEGylated Graphene oxide NPs	25, 27, 50 nm PEGylated 450 nm negatively charged	Healthy mice	450 nm non-PEGylated formed aggregates in the abdomen, the PEGylated particles were cleared mainly to the liver and spleen	[60]
PLGA	265 nm negatively charged	Healthy mice	NPs were cleared from the abdomen within 2 days and accumulated in the spleen and liver	[61]
Gelatin NPs loaded with Paclitaxel	60, 90 nm	Nude mice bearing human xenograft tumor model - pancreatic Hs766T tumor cells	Rapid clearance (within 24 hours) of the NPs from the abdomen and poor efficacy *in vivo* compared with MPs	[62]
Egg lecithin liposomes encapsulating [^{14}C] sucrose	48, 170, 460, and 720 nm	Healthy rats	Rate and extent of absorption from the peritoneal cavity was independent on size. The Smallest liposomes accumulated in lymph with little lymph node retention, larger liposomes were collected in the lymph nodes	[63]
Liposomes encapsulating doxorubicin (different lipid composition)	150, 605 and 4225 nm negatively charged liposomes	CDF$_1$ mice bearing Ehrlich ascites carcinoma tumors	Lipid composition did not affect the clearance of the liposomes. Large liposomes were superior over the small liposomes and free drug	[64]

			solution in inducing cytotoxicity	
99mTc DSPC/CHOL liposomes	100, 400, 1000 and 3000 nm neutral liposomes	Healthy mice	Highest peritoneal concentration was measured for the 1000 nm liposomes. The 3000 nm sedimented upon abdominal organs	[65]
PEGylated and non-PEGylated liposomal formulations	100 and 1000 nm PEGylated, cationic and negatively charged liposomes	Healthy mice	Positively charged liposomes of 1000 nm exhibited the highest retention time in the peritoneal cavity	[66]
[14C] Polyacrylic polymeric particles composed of carbon-14 polyhexylcyanoacrylate nanoparticles (PHCA) and polymethylmethacrylate (PMMA)	543 nm for PHCA and 1.4 µm for PMMA	Healthy rats	Targeting the lymphatics via the IP route was 70-2000 fold higher when compared to the IV route	[68]

4.3.2. The size dilemma for optimal tumor penetration of NPs

To ensure maximal efficacy of cytotoxic drugs, penetration of the drug deep into the tumor tissue is crucial. From a clearance point of view, ideally, large particles (above 1 µm) such as MPs and microspheres are used as depot systems to prolong the retention time of drugs in the peritoneal cavity. In this respect, different MPs loaded with chemotherapeutics were used for the treatment of abdominal cancer [49, 69, 70]. Nevertheless, it has been shown that micro-sized formulations bear the risk of inducing peritoneal adhesions and inflammations [4, 61, 71]. The optimal balance between retention time, adhesions and efficacy of MPs is currently a topic of interest for several research groups [72].

With regard to nanomedicines, the size dilemma consists of having a delivery system that efficiently penetrates on the level of the tumor, but on the other hand, also sufficiently remains present in the IP

cavity for this penetration to take place. The poor retention time of chemotherapeutics and nanomedicines in the abdomen, however, is expected to limit peritoneal tumor penetration and anti-tumor activity of these nanomedicines. Also, the microenvironment of many solid tumors makes the penetration of drugs very difficult or even impossible in some cases [73]. Tumors are characterized by a dense extracellular matrix, limiting the penetration not only of cytotoxic drugs but also of nanomedicines [74]. Also, the abundant and leaky vasculature in tumors results in a high interstitial fluid pressure (IFP) which counteracts the penetration of drugs and nanomedicines into the tumors by convective flow [75]. It has been demonstrated that smaller sized nanomedicines penetrate into tumors more efficiently than larger ones [76, 77]. Apart from the size of the nanomedicines, it has been recently shown that the surface charge plays a very important role in tumor penetration. Wang et al. [78] provided a strong experimental evidence in different tumor models that 100 nm positively charged PEGylated nanomedicines are superior in terms of tumor penetration over their neutral and anionic counterparts, and consequently exhibit enhanced tumor killing efficiency. In the context of NPs penetration into peritoneal tumors, Ding et al. [79] studied the antitumor efficacy and tumor penetration of 100 nm negatively charged (at pH 7.4) cisplatin-loaded gelatin-poly(acrylic acid) NPs in mice bearing hepatic H22 tumors. The nanoparticulate system significantly decreased the tumor volume when compared to the cisplatin solution. However, tumor sections obtained 2 days following IP administration, showed that NPs are not able to effectively permeate the tumor deeply, but rather affect the cells near the vasculature. This suggests that IP injected NPs first entered the systemic circulation before reaching the tumor site. On the other hand, a recent study demonstrated that nanoscale PTX-polymersomes [80, 81] were detected deep inside the tumor's parynchema, indicating efficient tumor penetration [82] . Interestingly, the fluorescence signal showed higher accumulation of PTX-polymersomes in tumors compared with other organs (lung, kidney, heart, liver and spleen). Following IV administration, however, PTX-polymersomes accumulated less in peritoneal tumors and more in other organs. Overall, the data suggest that NPs penetrated into the tumor nodules both (1)

directly, from the IP cavity and (2) systemically after clearance from the IP cavity, so that both small poorly vascularized and large vascularized tumors are affected by the drug.

A possible strategy to lower the IFP is to decrease the vasculature in tumor nodules. It has been recently shown by Gremonprez et al. [83] that the inhibition of VEGF by Bevacizumab enhances the penetration of chemotherapeutics into peritoneal tumors and inhibits tumor growth in mice bearing colorectal carcinomatosis. Whether the tumor penetration of nanomedicines would also improve upon inhibition of VEGF remains to be investigated. However, given the important role of VEGF in the angiogenesis and formation of ascites [8, 9] (see section 2.), VEGF inhibitors seem excellent candidates for the treatment of peritoneal metastatic cancer. Albendazole (ABZ) is a widely investigated anti-parasite drug for its ability to inhibit VEGF [84], as well as tumor growth via the inhibition of tubulin polymerization and G2 M phase of the cell cycle. Noorani et al. [85] formulated ABZ bovine serum albumin (BSA) NPs of respectively 7-10 nm and 200-250 nm for the sustained release of ABZ in the peritoneum. The anti-tumor efficacy of both formulations following IP injection was tested *in vivo* in OVCAR3 xenograft tumor model. The 10 nm ABZ BSA particles significantly suppressed the tumors at a much lower dose than the free drug, whereas non-significant tumor inhibition compared with free drug was observed for the 200 nm ABZ BSA. Yet, both formulations significantly reduced the ascites volume and number of malignant ascites cells in the abdomen of the treated nude mice. The authors attributed the significant decrease in tumor burden between both formulations to the penetration of NPs into the tumor tissue, which is highly likely more pronounced for the 10 nm ABZ BSA. Therefore, it seems that smaller NPs are beneficial for optimal tumor penetration, in spite of the short residence time expected in the peritoneal cavity.

5. Strategies for IP delivery and sustained release of nanomedicines in the peritoneal cavity

Possible strategies to enhance the biodistribution and residence time of nanomedicines in the peritoneal cavity are depicted in table 2 and Figure 4. As mentioned above, for most NPs rapid

clearance from the peritoneum to the systemic circulation takes place. Therefore, to overcome the obstacles associated with intraperitoneally injected nanomedicines as such (i.e. dispersed in solution), release of NPs in a sustained manner in the peritoneum seems an optimal solution (Figure 4B, 4E). Conceptually, controlled release of small doses of NPs loaded with anti-cancer therapeutics, nucleic acids or a combination of both from depot systems could attenuate lymphatic drainage of the NPs, prolong the retention time in the abdomen, increase the exposure time of the tumors with the drug, and as a result augment its efficacy (see table 2). Aiming to increase the residence time of platinum (Pt) in the peritoneal cavity for the local treatment of ovarian cancer, Cho et al. encapsulated Pt within Hyaluronic acid (HA) NPs forming PtNPs [86]. These NPs were then loaded on a biocompatible and biodegradable *in-situ* crosslinkable HA gel (PtNP/gel). Both systems (PtNPs and PtNP/gel) showed *in vitro* sustained release kinetics of Pt, and *in vivo* drug release for the PtNP/gel depot system of less than 2 weeks in the peritoneal cavity. Unexpectedly, when these systems were IP instilled in the abdomen of mice bearing SKOV-3 tumors, no enhancement in anti-tumor efficacy was measured compared with a solution of the free drug (i.e. cisplatin solution) [86]. Therefore, these findings do not support the expected synergy between the residence time of the drug and its therapeutic effect. The same research group evaluated the efficacy of PTX nanocrystals and microparticulate PTX precipitates loaded on a similar crosslinkable HA hydrogel for the treatment of mice bearing SKOV-3 ovarian cancer tumors [87]. Contrary to outcomes obtained with the PtNP/gel, the PTX nanocrystals exhibited significant tumor suppression upon single IP administration compared with the commercially available Taxol®. The microparticulate PTX precipitates, did not, however, result in a significant tumor inhibition compared with Taxol®. Since both studies were performed with the same depot system (i.e. HA hydrogel) and cancer model, the differences in efficacy between the studies most probably arise from the PK properties of the drug encapsulated within the hydrogel. In particular, PTX, with a molecular weight of approximately 854 Da and a bulky structure, is probably cleared slowly from the peritoneal cavity [88], resulting in increased exposure to peritoneal tumors. Indeed, when compared with a lower molecular weight platinum-

based compound, PTX exhibited the highest peritoneal-to-plasma area under curve (AUC) ratio [89].

Importantly, a high peritoneal-to-plasma AUC ratio is not always translated in enhanced antitumor activity, since drug penetration also plays an important role [90]. Rangrang et al. [91] did find that sustained release of NPs from a hydrogel may hold a promise for future clinical applications. A thermosensitive hydrogel (i.e. liquid at room temperature, gel at the body temperature) composed of polylactic acid and Pluronic L64, co-encapsulating NPs loaded with the anti-cancer agent docetaxel and the anti-microbial tumor suppressing peptide LL37 (Figure 4B), significantly inhibited tumor growth in a mice model derived from colorectal cancer HCT116 cells following IP administration. This significant inhibition was accompanied by an increase in the survival of the treated mice when compared with a solution containing both drugs and the hydrogel containing only docetaxel NPs. Similarly, Xu et al. [92] developed a thermosensitive hydrogel assembled by PTX NPs of amphiphilic copolymer, termed as PTX/PECT^{gel} [93]. Upon IP administration of PTX/PECT^{gel} in mice bearing CT26 colorectal peritoneal carcinomatosis model, the hydrogel degraded over 8 days in the peritoneal cavity and significantly decreased the tumor weight compared with the free PTX solution – Taxol®. Furthermore, the authors showed higher abdominal PTX concentration for the PTX/PECT^{gel} compared with Taxol® for an extended period of time.

Another possible interesting strategy to improve the biodistribution of nanomedicines in the peritoneal cavity is, similarly to the PIPAC method described in section 3.2., the aerosolization of nanomedicines in the peritoneum (Figure 4C). In theory, nanomedicines can be nebulized in the peritoneal cavity. Whether or not the nanomedicines' structure or function are affected by the high pressure nebulization, however, remains to be elucidated.

In contrast to PIPAC, NPs have already been used in the setting of (H)IPEC (Figure 4D). In a recent study by Nowacki et al.[94], HIPEC was performed in mice using a nano-sized drug delivery system based on carbon nanotubes (CNTs) [95]. Briefly, CNTs loaded with cisplatin were functionalized with the anti-CD133 antibody to reduce the resistance to chemotherapy, emerging from the CD133 antigen. When

the CNTs functionalized with anti-CD133 were applied IP via the HIPEC procedure in the abdomen of mice bearing peritoneal B16 melanoma tumors, the best general survival (12.6 days) observed was for the functionalized CNTs, and the shortest general survival (8 days) was for the mice in which the HIPEC procedure was not carried-out [94]. Likewise, De Smet et al. [96] investigated the suitability of PTX nanosuspension stabilized by Pluronic F127® for HIPEC treatment in rats bearing SKOV-3 ovarian cancer. Compared with the commercially available PTX formulation - Taxol®, no significant tumor volume reduction was documented 7 days and 14 days after HIPEC treatment. A significant reduction in tumor volume was, however, observed when the PTX nanosuspension was compared with the non-treated group. Also, the rats treated with the PTX nanosuspension recovered faster following the HIPEC procedure.

Overcoming the resistance of cancer cells remains one of the main hurdles in cancer therapy [97]. In many cancer patients, even after complete remission, a relapse can occur due to multi-drug resistant (MDR) tumors. One approach to limit drug resistance is to minimize the periods between drug doses. In addition to the localized delivery strategies aiming to enhance the exposure of tumors to chemotherapeutics, metronomic dosing represents a novel approach defined as the frequent and continuous administration of conventional chemotherapy drugs at low doses without drug-free breaks (Figure 4E) [98]. Goldberg and coworkers developed slow-release drug delivery systems based on dual layer surface coating of PLGA PEGylated NPs loaded with PTX for IP treatment of mice bearing BR5FVB1-Akt drug resistant ovarian cancer tumors. Compared with free PTX, metronomic dosing obtained by sustained release of PTX in the peritoneum significantly prolonged the survival of the treated animals [99]. A synergy in anti-tumor activity was documented when metronomic dosing was achieved with PLGA-PRINT NPs encapsulating docetaxel in combination with the antiangiogenic complex of chitosan NPs loaded with the enhancer of zeste homolog 2 (mEZH2) siRNA in HeyA8 and SKOV3ip1 ovarian tumor models. The chemotherapeutic agent (i.e. PLGA-PRINT docetaxel) was IP administered, whereas the siRNA-NP complex was intravenously injected [100].

In addition to drug resistance, the lack of tumor specificity is a major obstacle in IP chemotherapy. Ideally, the nanomedicines should specifically accumulate at the target site, and leave healthy tissues unaffected. In general, this targeting can be accomplished by incorporating antibodies or targeting ligands at the NPs' surface to enhance the interaction between the NPs and the tumor site. The folate receptor alpha (FR-alpha) has already been identified as a suitable target for cancer therapy and imaging [101]. Also, VEGF and Human Epidermal Growth Factor Receptor 2 (HER2) targeted antibodies show potential for specific tumor targeting [102]. In these studies, the targeting moieties were coupled to fluorophores, to improve debulking in cytoreductive surgery after tumor-specific intraoperative fluorescence imaging. When a HER2 targeting antibody was coupled to PTX containing NPs, however, no difference in overall tumor accumulation between targeted and non-targeted NPs was seen [103]. It should be noted that due to the heterogeneous origin of primary tumors that can lead to PC, suitable targeting agents will greatly differ from patient to patient [104]. Therefore, a personalized medicine approach seems recommended, in which individual suitable tumor-specific targets can be identified and validated.
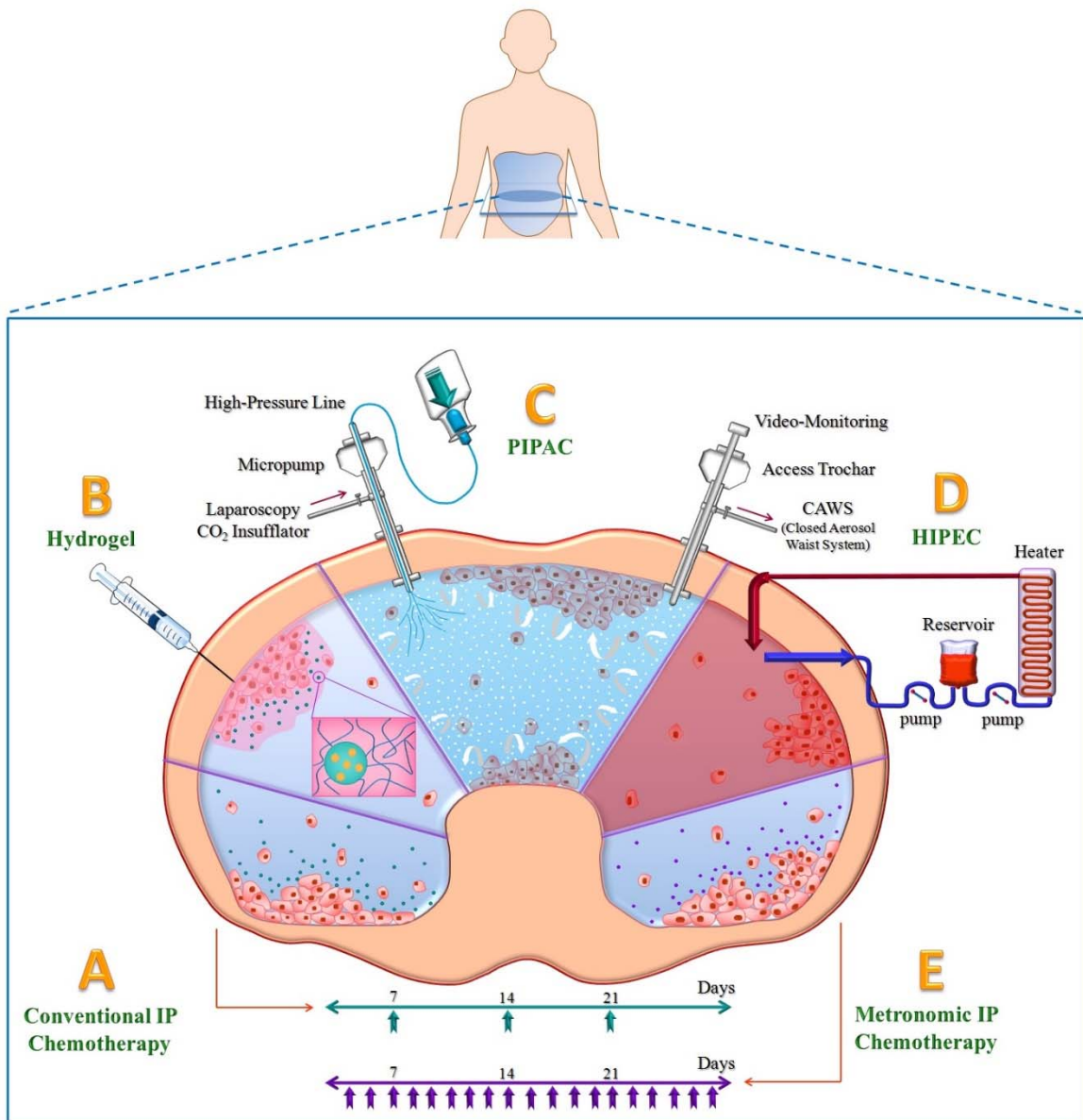
Figure 4. Schematic illustration of the different therapies involving nanomedicines from left to right.

(A) NPs loaded with chemotherapeutics or other macromolecules**. (B)** Sustained release of NPs loaded with anti-cancer drugs from a depot system (e.g. hydrogel). **(C)** Nebulization of NPs using PIPAC. **(D)** HIPEC of NPs. **(E)** Continuous administration of NPs loaded with chemotherapeutics at low doses without drug-free breaks known as metronomic therapy.

Table 2. Investigated IP administered formulations to overcome the rapid clearance of nanomedicines in solution following IP injection

Formulation	Hydrodynamic diameter & surface charge (if available)	Cancer model	Outcome	Reference
Bovine serum albumin NPs encapsulating ABZ	~ 10 nm ~ 200 nm	Nude mice bearing OVCAR3 tumors	Significant reduction in the ascites fluid volume, as well as in the VEGF expression	[85]
Pt solution, PtNPs and PtNPs loaded on HA hydrogel	PtNP – 270 nm, negatively charged	Balb/c mice bearing SKOV-3 ovarian cancer tumors	Pt solution was superior over the PtNPs and PtNP/gel in terms of tumor inhibition	[86]
PTX nanocrystals and microparticulate PTX loaded on HA hydrogel compared with the commercially available PTX formulation – Taxol®	PTX nanocrystals – rods shaped ~ 260nm and a surface charge of -6 mV, microparticulate PTX – needle shaped ~ 11.5 µm in length and 2 µm in width, negatively charged (-3mV)	Balb/c mice bearing SKOV-3 ovarian cancer tumors	PTX nanocrystals loaded on the HA hydrogel, but not the microparticulate PTX, significantly prolonged the survival of mice compared with the commercially available PTX formulation - Taxol®	[87]
PLA-L35-PLA NPs loaded with docetaxel and LL37 formulated into PLA-L64-PLA thermosensitive hydrogel	PLA-L35-PLA NPs ~ 130 nm, neutral NPs	HCT116 peritoneal carcinomatosis model	Sustained release of docetaxel and the suppressing peptide LL37 efficiently suppressed the growth of peritoneal carcinomatosis in mice	[91]
Thermosensitive hydrogel assembled with PTX nanoparticles (PTX/PECT^{gel})	PTX/PECT NPs ~120 nm	Mice bearing CT 26 colorectal peritoneal carcinomatosis model and ascites fluid	IP administration of PTX/PECT hydrogel efficiently inhibited tumor growth and metastasis compared with Taxol®	[92]

Carbon nanotubes (CNTs) loaded with cisplatin and functionalized with the CD-133 antibody	NA	IP B16 melanoma tumors	Longer survival (12.6 days) was obtained for CNTs delivery systems after HIPEC compared to the situation where HIPEC was not carried-out	[94]
Nanocrystalline PTX stabilized by Pluronic F127®	~ 400 nm	Rats bearing SKOV-3 ovarian cancer tumors	HIPEC treatment using the PTX nanosuspension resulted in a significant tumor suppression compared to the non-treated group. No significant reduction in tumor growth was observed when the PTX formulation was compared to the commercially available Taxol®	[96]
Dual-layer surface PLGA PEGylated NPs loaded with PTX for metronomic dosing	~150 nm, negatively charged	mice bearing BR5FVB1-Akt drug resistant ovarian cancer tumors	Significant increase in the survival of mice compared to the free drug	[99]
PLGA-PRINT docetaxel NPs (IP administered metronomic dosing) and chitosan NPs complexed with mEZH2 siRNA (administered IV)	PLGA-PRINT docetaxel 80 x 320 nm 230 nm Negatively charged	HeyA8 and SKOV3ip1 ovarian tumors	Significant anti-tumor activity in both cancer models	[100]

6. Nanomedicines-based IP therapy – ongoing clinical trials

Here, we focus on two NP formulations that were evaluated for IP therapy in humans **(Table 3)**. A recent phase I study evaluated the toxicity, tolerability, and pharmacokinetics (PK) of intraperitoneally administered nanoparticulate Cremophor-free PTX (NanoTaX®) in 21 patients with peritoneal solid tumors malignancies, following CRS [105]. The selected patients received six escalating doses of

NanoTaX® (50-275 mg/m^2) every 28 days. Compared with the IV administered PTX, no additional increase in the toxicity was documented. Moreover, the treatment resulted in a favorable peritoneal PK profile, exhibited by peak concentrations of PTX in the peritoneal fluid that are 450-2900 folds higher than the peak concentrations of PTX in plasma 2 days following injection. Response was determined in 16 patients. Among those, four patients remained stable, while in twelve patients the tumors continued to grow (i.e. disease progression). Remarkably, five patients with advanced cancers survived more than 400 days after the beginning of the treatment. In summary, this study provided a clinical evidence in humans showing that NanoTax® administered via IP catheter exhibits lower systemic toxicity and higher levels of drugs in the peritoneal cavity compared with the IV administered PTX. This low toxicity and high peritoneal PTX retention is explained by the fact that NanoTax® is actually a 600-700 nm rod shaped reservoir which allows continuous release of PTX in the peritoneum. The study was completed in 2013 and it is unclear yet whether a subsequent phase II trial is planned.

The second NP-based formulation under clinical investigation for IP therapy in humans is Abraxane®. Abraxane® is a Cremophor®-free, albumin-based NP with PTX (~130 nm), used in clinical oncology for the treatment of metastatic breast and pancreatic cancer, as well as neoplasms. The Food and Drug Administration (FDA) and the European Medicines Association (EMA) approved Abraxane® for IV administration [106]. Abraxane® has however not been approved yet for use in IP therapy. A recent phase I trial [107] aimed to examine the maximally tolerated dose (MTD), adverse effects and PK of dose-escalating intraperitoneally administered (via IP catheter) Abraxane®. 27 patients with advanced peritoneal malignancies showed high peritoneal exposure of Abraxane® compared to the plasma exposure (i.e. pharmacologic advantage) with a low inter – and intra-patient variability.

Table 3. Ongoing clinical trials using nanomedicines for the IP treatment of peritoneal tumors

Formulation	Diameter	Clinical trial (phase/No. of patients)	Outcome	Reference
NanoTax® - nanoparticulate reservoir of PTX	Rod-shaped 600-700 nm	Phase 1 included 21 patients with peritoneal solid tumor malignancies after CRS	IP administration of NanoTax® results in high PTX levels, minimal systemic exposure and reduced toxicity compared with the IV administration	[105]
Abraxane® - albumin based NPs bound to PTX	~ 130 nm	Phase 1 included 27 patients with advanced peritoneal malignancy	Significant peritoneal exposure of Abraxane® compared to the plasma, low inter- and intra-patient variability	[107]

7. Conclusions and future perspectives

IP therapy for the treatment of peritoneal carcinomatosis is a rapidly growing niche that is being explored through an intensive effort of clinicians, pharmacologists and material scientists. To date, IP therapy of PC has not become a standard of care. An important aspect to take into account when developing IP therapies is to retain anti-cancer agents as much as possible in the peritoneal cavity, to achieve maximal tumor exposure to the drug. NPs are being utilized to deliver drugs to the peritoneum, however, when administered as such in dispersion, rapid clearance to the systemic circulation hampers their biological activity. Therefore, to unravel the potential of nanomedicines for IP therapies, future research should focus on improving the biodistribution of nanomedicines in the peritoneum, and correlate it with tumor accumulation, penetration, and killing efficacy. The balance between these is not easy to achieve in the peritoneal cavity. On one hand, the use of small nanomedicines (below 100 nm) would be very efficient for tumor penetration and maximizing drug efficacy. On the other hand, those small nanomedicines will highly likely be associated with a short residence time in the abdomen. In light of these limitations, it seems that injecting nanomedicines dispersed in a solvent will not be the optimal strategy for the treatment of PC. Nevertheless, to give a clear-cut answer whether the mission is possible with nanomedicines, in-depth investigation of the sustained release platforms described in this article, such as release of NPs from biodegradable hydrogels in the peritoneum and metronomic dosing is a prerequisite. Also, the identification and validation of tumor-specific targets will further help to develop targeting agents that increase tumor specificity of the nanomedicines. In addition, IP aerosol delivery (PIPAC) of nanomedicines or (H)IPEC of NPs as an adjunct to surgery may hold promise in selected patients.

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