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1 Drug delivery systems to prevent peritoneal metastasis after 2 surgery of digestives or ovarian carcinoma: A review.

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12 **Abbreviation list**

13 5-FU: 5-fluorouracil

14 AUC: Area under the curve

15 BMA: n-butyl methacrylate

16 CLA: Linoleic acid

17 CRS: Cytoreductive surgery

18 DDS: Drug delivery system

19 DMPC: L- α -dimyristoylphosphatidylcholine

20 DSPC: L- α -distearoylphosphatidylcholine

21 DTX: Docetaxel

22 EMA: European medicines agency

23 EPIC: Early post-operative intraperitoneal chemotherapy

24 FDA: Food and drug administration

25 HA: Hyaluronic acid

26 HA-CHO: aldehyde form of HA

27 HA-ADH: adipic dihydrazide modified HA

28 HIPEC: Hyperthermic intra peritoneal chemotherapy

29 IDA: Iminodiacetic acid

30 IP: Intraperitoneal

31 MA: Malonic acid

32 MP: Microparticle

33 MPC: 2-methacryloxyethyl phosphorylcholine

34 MS: Microsphere

35 NP: Nanoparticle

36 OX: Oxaliplatin

37 PCI: Peritoneal cancer index

38 PDPA: Poly(2-(diisopropylamino) ethyl methacrylate

39 PECE: Poly(ethylene glycol)-poly(ϵ -caprolactone)-poly(ethylene glycol)

40 PEG: Poly ethylene glycol

41 PEO: Polyethylenoxide

42 PLA: Polylactic acid
43 PLGA: Polylactic co-glycolic acid
44 PM: Peritoneal metastasis
45 PNIPAM: Poly(N-isopropylacrylamide)
46 POEGMA: Poly(oligoethylene glycol) methacrylate
47 PPO: Polypropylenoxide
48 PTX: Paclitaxel
49 RES: Reticuloendoplasmic system
50 TA: Tannic acid
51 Tf: Transferrin
52

53 **Abstract**

54

55 Peritoneum represents a frequent site of metastasis especially for digestive and ovarian primary
56 cancers. The conventional approach to treat peritoneal metastasis consists in systemic
57 chemotherapy, but the median survival associated is only a few months. Recent therapeutic
58 developments result in an aggressive strategy associating cytoreductive surgery (CRS) and
59 hyperthermic intra peritoneal chemotherapy (HIPEC). However, a recent study failed to show an
60 improvement in the overall survival and relapse free survival of this combo in comparison to CRS
61 alone. Confronted to a lack of guidelines, several drug delivery systems (DDS) had been developed
62 and tested in animal models to offer an effective easy-to-use solution for surgeons to prevent
63 peritoneal metastasis. In this work, we reviewed most of the strategies used to treat peritoneal
64 metastasis (PM) from digestive or ovarian origin and concentrated on 3 different DDS strategies:
65 particulates DDS, non particulates DDS (including implants, films and gels) and combination of both
66 (in particular hydrogels loaded with particles).

67

68 *Keyword: Drug delivery system; peritoneal metastasis; microparticle; nanoparticle; hydrogel;*
69 *thermogel.*

70 **1. Introduction**

71

72 The peritoneum is a single layer of squamous mesothelial cells closely connected together. The sub-
73 mesothelial layer supports the vascular network of blood vessels as well as lymphatics. This
74 connective tissue is also composed of collagen, adipose tissue, lymphocytes, fibroblasts and
75 macrophages (Albertine et al., 1982). Together, it constitutes a continuous serous membrane
76 composed of two layers, the parietal one covering the abdominal wall and pelvic cavities, and the
77 visceral one covering the outer side of the organs (Figure 1). Both layers delimit the peritoneal cavity
78 with a volume of fluids near 50 mL in healthy human (Sherwood, 2015). The peritoneal fluid is
79 composed of water, cells, electrolytes, antibodies, leukocytes exhibiting a physiological pH (Howard

80 and Singh, 1963). The peritoneum main function is to facilitate organs and viscera free movement by
81 preventing frictions and adherences.

82 Figure 1

83 It represents a frequent site of metastasis especially for digestive and ovarian primary cancers (Desai
84 and Moustarah, 2020). Peritoneal metastasis (PM) is often characterized by small nodules spread all
85 over the peritoneal surface, which can occur via natural metastasis process with cell dissemination,
86 invasion, adhesion, proliferation; or via iatrogenically by stalling cancer cells during surgical resection
87 of primary cancer, or other tumor perforations. The disease represented by carcinomatosis
88 apparition is associated with a limited survival of only a few months if untreated (Lambert and
89 Hendrix, 2018), (Sadeghi et al., 2000). The conventional approach to treat PM consists on systemic
90 chemotherapy, but the median survival associated is low and varies from 5.2 to 12.6 months for
91 colorectal origin (Koppe et al., 2006).

92 Two decades ago, a novel dual strategy treatment was introduced associating cytoreductive surgery
93 (CRS) with immediate hyperthermic intra peritoneal chemotherapy (HIPEC). Protocol consists in the
94 heating of one or several drugs such as mitomycin C, oxaliplatin, cisplatin or doxorubicin until 41-
95 43°C followed by administration in peritoneal cavity during 30 to 90 min depending on groups
96 (Turaga et al., 2014)(Sugarbaker, 2019) The rationale of this combination treatment is based on
97 surgical removal of macroscopic tumors, strengthened by local intraperitoneal (IP) chemotherapy
98 targeting the residual microscopic disease. Macroscopically complete CRS is a major prognostic
99 factor, with 5-year survival rates as high as 45% compared to less than 10% when CRS is incomplete
100 (Verwaal et al., 2008). The advantage of IP route results in the encirclement by peritoneum/plasma
101 barrier of peritoneal cavity, slowing clearance of drug which prolonged its contact in peritoneum,
102 with limitation of blood passage and systemic toxicity, allowing higher dose of drug administration
103 (Jacquet and Sugarbaker, 1996)(Van der Speeten et al., 2010). Verwaal et al proved the efficacy of
104 CRS + mitomycin HIPEC treatment in a randomized clinical trial with systemic chemotherapy alone as
105 comparison. The median survival was significantly prolonged in CRS + HIPEC arm (22.3 *versus* 12.6
106 months), making this aggressive strategy the current standard care for colon peritoneal metastasis
107 (Verwaal et al., 2003).

108 However, two pharmacokinetic problems appear to limit the effectiveness of IP therapy: poor tumor
109 penetration and no uniform IP distribution(Mohamed and Sugarbaker, 2003). Since recent
110 publication of PRODIGE-7 trial results on colorectal cancer, benefits of CRS + HIPEC gold standard of
111 care is questioned. 265 patients were randomized to CRS + HIPEC with oxaliplatin arm or CRS alone
112 arm. No significant difference in overall survival was found, with a median of 41.7 months in the
113 HIPEC arm vs 41.2 months in the non-HIPEC arm and no significant difference in relapse-free survival
114 (13.1 vs 11.1 months) (Quenet et al., 2019). Moreover, a recent study failed to prove the peritoneal
115 metastasis-free survival improvement at 18 months in patients with T4 or perforated colon cancer
116 after prophylaxis administration of oxaliplatin based HIPEC (Klaver et al., 2019).

117 IP route of drug administration is studied since many years. The absorption in blood circulation can
118 occur by two different ways: through capillaries or lymphatics depending on the molecule size.
119 Macromolecules are mainly taken up by lymphatic vessels then drained into lymph nodes and finally

120 join the venous circulation through thoracic and right lymphatic duct (Figure 2) (Miller, 1981),
121 whereas small molecule and solutes are absorbed by capillaries and drained to the portal vein
122 (Williams and White, 1986). The rate of peritoneal-plasma barrier passage depends on the
123 physicochemical properties of the drug, dissolution rate of the particle suspension in the peritoneal
124 cavity and particle size. Indeed, molecules have to cross several obstacle like mesothelium, basal
125 membrane, interstitium with bundle of collagen fibrils and blood vessel with glycocalyx, before
126 reaching systemic circulation (Flessner, 2008; Jacquet and Sugarbaker, 1996).

127 The efficacy of the IP chemotherapy still investigated in many clinical trials, and at the moment, there
128 is no consensus or guidelines on the treatment strategy of PM of colorectal origin, only expert
129 opinion (Abboud et al., 2019)

130 As a result, the need of alternative development strategies to prevent and treat PM is important to
131 resolve recurrence problems with successful outcomes. This real clinical need led to many
132 investigations since more than thirty years. Several drug delivery systems (DDS) had been developed
133 and tested in animal models to offer an efficient and easy solution to use for surgeons to prevent
134 PM. We propose to review them in the following of the article.

135 **2. Particulate drug delivery systems used in IP route**

136 Administration of cytotoxic drugs intraperitoneally represent a multiple challenge reflected by a lack
137 of formulations approval for this administration route. The molecular structure of the cytotoxic
138 influences its behavior in the peritoneal cavity: small and hydrophilic drugs are rapidly absorbed in
139 the blood circulation leading to hematologic or systemic side effects (cisplatin (István Rusznyák et al.,
140 1967), 5-fluorouracil (Speyer et al., 1980)), while high molecular weight or hydrophobic ones induce
141 local toxicity and dose-limiting effect (Taxol® (Markman et al., 1992; Morgan et al., 2003), docetaxel
142 (Morgan et al., 2003)).

143 While there is not only one delivery system for these drugs with various physical properties, one can
144 still draw the ideal properties of a DDS dedicated to IP carcinoma: i) remain stable in the peritoneal
145 cavity, ii) release high concentration of chemotherapeutic locally in the peritoneal cavity to have a
146 therapeutic effect and tumor penetration, iii) avoid the formation of adherences, inflammation or
147 local toxicity, iv) prolong the release of the drug over at least one week to avoid tumor implantation,
148 v) limit systemic passage to avoid side effects.

149 **2.1 Microparticles**

150 This is the most studied drug delivery system (Table 1). One key parameter is their size ($> 1 \mu\text{m}$)
151 which determines their release, their residence time in the peritoneal cavity and their systemic
152 passage. Comparing various DDS, Tsai et al. showed that after IP injection, paclitaxel release from
153 microparticles (MP) (about $4 \mu\text{m}$) was about 70% in 24 h while it was 90% in 2 h for gelatin
154 nanoparticles of 660 nm (Tsai et al., 2007). The authors proposed a schematic explanation of two
155 major elimination pathways from the peritoneal cavity: absorption through the peritoneum of the
156 free drug or lymphatic drainage for corpuscular DDS with lymph node blockage as a function of the
157 size (Figure 3). Basically, bigger was the DDS longer was the residence in the peritoneal cavity.

158 As regard to the size, a more homogeneous distribution was obtained with small MP made of
159 poly(D,L-lactide-co-glycolide) ($4 \mu\text{m}$) as compared to bigger ones ($30 \mu\text{m}$) which stayed near the
160 injection site (Lu et al., 2008). $4 \mu\text{m}$ is the smallest size which can be envisioned to avoid rapid

161 clearance of MP through subdiaphragmatic pores (3 μm) (Lu et al., 2008). This value remains
162 unprecise because other median and mean values are trackable in the literature (5-6 μm (Simer,
163 1948) or 2.8-3.5 μm (Tsai et al., 2007)). Their MP formulation called “tumor priming technology” was
164 designed to have two release phases: a first rapid one to enable cancer cells apoptosis with a 70%
165 release of paclitaxel at day 1 (polymer ratio 50:50 Lactide:Glycolide), then a slower release phase
166 corresponding to 1% paclitaxel release each day (polymer ratio 75:25 Lactide:Glycolide). This
167 technology enabled with a single drug administration, a better MP tumor uptake, lower host toxicity
168 and a better therapeutic efficacy feed through prolonged survival (Lu et al., 2008).

169 Liggins et al. also analyzed two size range 10-40 μm and 30-120 μm of poly (L-lactic acid) MP and
170 highlighted the presence of small MP (10 μm) in the mediastinal lymph nodes after intraperitoneal
171 administration. They chose to carry their study with bigger MP in order to maintain them in the
172 peritoneal cavity. The cumulative release of Liggins’s formulation was considerably slower compared
173 to Lu and Tsai studies, with a total amount of paclitaxel reaching 25% 30 days after IP administration.
174 The efficacy of this DDS was proved by the absence of tumor nodules neither ascites in the MP
175 treated group 6 weeks after administration, in contrast with the no treated control group (Liggins et
176 al., 2000).

177
178 Another critical component in the management of MP release is the polymer choice. It must be
179 biodegradable, biocompatible and nontoxic. The principal polymer used is poly lactic acid (PLA)
180 combined or not with acid glycolic (PLGA). PLA and PLGA are approved by the U.S. Food and Drug
181 Administration (FDA) and used in many medical devices as surgical sutures, implants, prostheses
182 (Athanasidou et al., 1996)... Hagiwara et al. designed 5-fluorouracil (5-FU) PLGA MP of 24 μm diameter
183 and analyzed 5-FU concentration in omentum and mesentery during 16 days. For both, 5-FU was
184 significantly higher with a 39 to 1153 folds ratio compared to 5-FU solution. Moreover, a small
185 amount of 5-FU was found in plasma for the MP treated group causing a systemic toxicity reduction
186 about 41.5% as regard to the solution group (Hagiwara et al., 1996). Kumagai et al. also
187 demonstrated a decrease in systemic toxicity with cisplatin encapsulated in PLGA MP. Cisplatin
188 concentration in kidney, liver and plasma were lower with MP formulation than cisplatin solution.
189 This was in correlation with an improvement of mean survival around 74 days for rats treated with
190 cisplatin MP compared with 48 and 9 days for cisplatin and saline solutions respectively (Kumagai et
191 al., 1996).

192 Some authors chose to combine various polymers in order to improve the MP formulation
193 properties. Fan et al. used Pluronic®, consisting of poly(ethylene oxide) (PEO) and poly(propylene
194 oxide) (PPO) blocks with a PEO–PPO–PEO arrangement, and PLA. Pluronic® brings strong affinity
195 toward small intestines and high permeation to the cell membrane. The MP obtained measured
196 around 45 μm and were spherical and porous allowing a cumulative release of 60%, 14 days after
197 treatment. Results indicated that DTX MP could induce more tumor cell apoptosis, and better
198 suppressed tumor cell proliferation as compared to DTX solution (Fan et al., 2014).

199 Gelatin MP were considered to enable a release mediated with gelatinases secreted in the tumor
200 microenvironment. Cisplatin (Gunji et al., 2013) and paclitaxel (De Clercq et al., 2019) prolonged the
201 effect of the chemotherapy while reducing their toxic effects. The optimal dose of paclitaxel to
202 achieve a good survival without drug related toxicity was evaluated by authors between 7.5 to 15
203 mg/kg (De Clercq et al., 2019). Taken together, those promising results compel authors to continue
204 with pharmacology and toxicology studies prior to begin a first-in-human phase I trial.

205 Finally, in a phase I trial, Armstrong et al studied the sustained release of paclitaxel MS (Paclimer®) in
206 peritoneal cavity of 13 patients suffering from ovarian cancer. MS of Paclimer® were made by the
207 incorporation of paclitaxel in a biodegradable polyphosphoester polymer matrix. Approximately 800
208 cm³ of warmed normal saline (30°C) was administered with the paclitaxel MS. The starting dose of
209 paclitaxel MS was 60 mg/m². Thanks to a prolonged release, the treatment was administered every 8
210 weeks for two cycles. Unfortunately, the pharmaceutical development of Paclimer® MS was stopped,
211 thus only 1 patient received 2 cycles of treatment and the maximum tolerated dose was not reached.
212 To note, one patient developed extensive, diffuse adhesions completely obliterating the peritoneal
213 space in the lower abdomen and pelvis moreover, foreign body giant cell reaction with residual
214 polymer filaments was found (Armstrong et al., 2006).

215
216 As a result, MP DDS seems to be effective in PM treatment on animals' models, depending on
217 disease stage and MP formulation. However, the main challenge still remains the safety
218 management. Indeed, it was well established that MP can induce inflammation and risk of adhesion.
219 Kohane et al. demonstrated the implication of the size and polymer molecular weight in this process.
220 They showed residues of closely apposed MP surrounded by a capsule of granulation tissue and early
221 fibrosis attesting inflammatory reactions (Kohane et al., 2006). Tabata et al. demonstrated also that
222 small MP (5µm) could be phagocytosed and induced a vigorous chemotactic response from cytokine
223 release and subsequent inflammatory reaction to the adjacent tissues (Tabata and Ikada, 1990).
224 Authors added that MP made with lower molecular weight polymers and nanoparticles appeared
225 considerably safer in terms of reduction of the adhesion risk.

226 2.2 Nanoparticles

227 Paclitaxel is a hydrophobic cytostatic drug solubilized by Cremophor EL® in its commercial
228 formulation (Taxol®). As Cremophor EL® is well known to induce toxicity (Gelderblom et al., 2001;
229 Weiss et al., 1990), De Smet et al. proposed a nanocrystalline suspensions of paclitaxel solubilized in
230 Pluronic F127®, forming nanoparticles (NP) of 400 nm diameter. No significant differences on tumor
231 growth were measured at day 7 & 14 after 45 min HIPEC between Taxol® and NP suspension (De
232 Smet et al., 2012). This is consistent with the limited drug penetration in tumor described by Fujiwara
233 et al. involving a treatment efficiency of IP chemotherapy only if micro metastases or tumor < 5mm
234 are considered (Fujiwara et al., 2007). Another formulation of paclitaxel formed by copolymerization
235 of 2-methacryloxyethyl phosphorylcholine (MPC) and n-butyl methacrylate (BMA) was proposed
236 (Soma et al. 2009). These co-polymers, forming NP around 50 nm, led to a significant decreased of
237 tumor growth and prolonged survival compared with paclitaxel dissolved in Cremophor EL® solution
238 *in vivo* (Soma et al., 2009). Evaluating the route of administration, they assessed a higher
239 accumulation of the nanoparticles after i.p. injection as regard to i.v.. Kamei et al. observed that after
240 i.v. injection, NPs were restricted to peripheral area, while i.p. administration allowed deeper
241 paclitaxel infiltration within the tumor and in the tumor nodule (Kamei et al., 2010).

242 Kamei et al. worked on peritoneal tumor measuring 2-3 mm. This team developed paclitaxel NP
243 formed by copolymerization of 2-methacryloxyethyl phosphorylcholine (MPC) and n-butyl
244 methacrylate (BMA). Authors demonstrated the ability of NP to infiltrate until 1 mm inside the tumor
245 nodule after 48 h contact compared to paclitaxel Cremophor EL® solution only found at 200 µm from
246 the tumor surface. However, Kohane et al. reported a strong localization of NP in the spleen
247 suggesting they were not suitable for drug release in peritoneal cavity (Kohane et al., 2006). This

248 limitation could explain the limited amount of cytotoxic reaching the tumor with traditional NP
249 needing further development.

250
251 In 2008, FDA approval was delivered to another formulation of paclitaxel consisting in albumin NP
252 (Abraxane® i.e. nab-paclitaxel) measuring 130 nm in diameter. Albumin is well tolerated, crosses
253 natural physiological barriers thanks to receptor mediated transcytosis and enhanced permeability
254 and retention effect (Yu and Jin, 2016). Moreover, it is devoid of surfactant such as Cremophor EL®,
255 therefore, leading to increased tissue distribution and decreased side effects (Yardley, 2013). The
256 penetration of paclitaxel in peritoneal cavity tissues was studied after a 60 min HIPEC procedure.
257 Using mass spectrometry, paclitaxel was only detected when using Abraxane® whereas no paclitaxel
258 was observed with Taxol®. This was confirmed by the pharmacokinetics results. The paclitaxel
259 concentration found in the peritoneal cavity of rabbits was $13.22 \pm 0.97 \mu\text{g/g}$ for Abraxane®
260 compared to $3.55 \pm 1.75 \mu\text{g/g}$ for Taxol® (Coccolini et al., 2017). Those results were consistent with
261 the one obtained by Kinoshita et al. who demonstrated a better antitumor activity of Abraxane®
262 compared to Taxol® on PM of gastric cancer after IP injection of equitoxic doses of paclitaxel in a
263 murine model ($p < 0.05$) (Kinoshita et al., 2014). The interest of Abraxane® encouraged Van de Sande
264 et al. to use it as PM treatment in a phase I first-in-human study for patients with upper
265 gastrointestinal, breast, or ovarian cancer, using pressurized intraperitoneal aerosol chemotherapy
266 (Van De Sande et al., 2018).

267 Innovative NP were also proposed, such as NP with expansile properties allowing NP size to swell
268 from 100 nm to 1000 nm reducing their clearance. These NP made with acrylate-based polymer and
269 a trimethoxybenzaldehyde derivative, allowed polymer expansion and paclitaxel release at acidic pH
270 only ($\text{pH} \leq 5$). After IP injection, NP showed a minimal release of paclitaxel at physiologic pH and
271 began to swell after exposition to acidic pH found intracellularly. The release was slow and prolonged
272 with 4% delivered to the peritoneal cavity per hour over 24 h and persisted several days after
273 injection. Another advantage of these NP was their ability to target tumor sites with a preferential
274 localization in endosomes, where pH is acidic. Those qualities resulted in upper antitumoral
275 efficiency compared to Taxol® and non-expansile NP, showing both total tumor mass and cumulative
276 disease severity score decrease, and mice survival improvement ($p < 0.005$) (Colson et al., 2011).
277 Authors did not find any toxicity neither adhesion nor obstruction relative to their NP. In 2013,
278 Gilmore et al. tested those promising expansile NP in a mice model undergoing debulking surgery. No
279 significant recurrence was observed in expansile NP group whereas more than 40% ($n=7$) were found
280 in the Taxol® solution group (Gilmore et al., 2013).

281 Targeted nanoparticles were also proposed in particular to target the folate receptor or HER2. PLGA
282 NP loaded with paclitaxel targeting the folate receptor showed improved mice survival as compared
283 to mice receiving untargeted NP ($p = 0.01$) (Werner et al., 2011). Polymeric poly (DL-lactic acid) NPs
284 targeting HER2 with the antibody Herceptin® (Trastuzumab) showed a better response with NP-
285 Herceptin® compared to free paclitaxel solution at the end of the IV/IP alternated protocol treatment
286 but unfortunately no complete recovery was observed in any treated mice. The biodistribution
287 experiment demonstrated that a majority of NP was found in the spleen, independently of the NP
288 administration mode (Cirstoiu-Hapca et al., 2010). This is consistent with Kohane et al. findings,
289 which could explain the relapse following the treatment sequence (Kohane et al., 2006).

290

291 NP seems to be an interesting DDS allowing deep infiltration in tumor with an antitumor efficacy
292 which can be enhanced by the functionalization of the NP surface with targeting ligands (Table 2).
293 However, the main challenge is to avoid the rapid localization in the spleen attenuating the cytotoxic
294 effect of drug contained inside.

295 2.3 Micelles

296
297 Micelles have been less studied in the context of IP. Nevertheless, few examples are reported below.
298 Core-shell-type polymeric formulation was obtained by the association of PEG as hydrophilic
299 component and hydrophobic polyaspartate. These micelles of 85 nm with paclitaxel enclosed in the
300 core, exhibited a significantly higher peritoneal nodules number and weight reduction as compared
301 to paclitaxel-Cremophor EL[®] solution, with no difference in toxic side effects. A high concentration of
302 paclitaxel was found in peritoneal nodules early after IP administration due to rapid enhanced
303 penetration of nanomicelles. However, paclitaxel was cleared from peritoneal cavity more rapidly
304 with nanomicellar solution as compared to paclitaxel-Cremophor EL[®] solution, leading in increased
305 its concentration in plasma. The superiority of C_{max} and AUC_{0-48h} in plasma of paclitaxel nanomicelles
306 could also explain their significant better efficiency in reducing weight and volume of subcutaneous
307 tumors thanks to a systemic effect (Emoto et al., 2012).

308
309 Gong et al. developed as well nano micelles for peritoneal use. They encapsulated doxorubicin in a
310 biodegradable and biocompatible poly (ethylene glycol)–poly(ε-caprolactone)–poly (ethylene glycol) (PECE)
311 copolymer leading to 30 nm spherical micelles. PECE copolymer had a temperature-sensitive
312 behavior, when temperature increased (>25°C), micelles size increased turning in a flexible and
313 during gel at body temperature in 20s. This property was supposed to offer a promising dual
314 antitumor and anti-adhesion effect in peritoneal cavity. *In vitro* release study revealed a cumulative
315 release about 52% at day 14 reaching a plateau at day 7. The therapeutic effect of doxorubicin-
316 micelles on colorectal peritoneal metastasis mouse model was significantly higher considering the
317 number and weight of tumor nodes compared to the doxorubicin solution group ($p < 0.001$).
318 Additionally, doxorubicin-micelles proved an integral neo-mesothelial cell layer formation of the
319 injured parietal and visceral peritoneum in 5-7 days without concerns of further adhesion formation
320 (Gong et al., 2012b).

321 Taken together, those results proved a real interest of this DDS, which might improve simultaneously
322 intraperitoneal chemotherapeutic effect and preventing peritoneal adhesions post-surgery.

324 2.4 Polymersomes

325
326 Polymersomes are a class of artificial vesicles formed by the self-assembly of amphiphilic block
327 copolymers. It can encapsulate water-soluble components in its hydrophilic core and water-insoluble
328 components in its hydrophobic surface. This nano-supramolecular structure can be made of
329 biodegradable polymers making them potentially interesting DDS. Simòn-Gracia et al. chose poly
330 (oligoethylene glycol methacrylate) (POEGMA) as hydrophilic polymer, and poly(2-(diisopropylamino)
331 ethyl methacrylate) (PDPA) as hydrophobic polymer yielding a pH-sensitive structure encapsulating
332 paclitaxel. At physiological pH 7.4, no paclitaxel was found in the cell culture medium, whereas at pH
333 6 polymersomes disassembled leading to the drug release (Simon-Gracia et al., 2016). After

334 peritoneal administration of paclitaxel-polymerosomes, the authors showed selective accumulation
335 and penetration of paclitaxel in peritoneal lesions simultaneously in periphery or deeper in tumor's
336 parenchyma. This suggests that polymerosomes reached tumor using both direct penetration and
337 systemic routes enhancing drug delivery capacity compared to IV route. Additionally, paclitaxel
338 polymerosomes demonstrated a better efficiency in the treatment of mice bearing peritoneal MKN-
339 45P gastric tumors compared to Abraxane® and paclitaxel-Cremophor EL® solution with a shrank
340 tendency observed after the first day of treatment (Simon-Gracia et al., 2016).

341 **2.5 Liposomes**

342 Liposomes are another kind of nanovehicles with a size ranging from 100 to 1000 nm employed as
343 DDS in the peritoneal cavity. The main advantage of those DDS is an absence of toxicity and
344 antigenicity thanks to their formulation, containing endogenous lipid such as cholesterol or lecithins.
345 As early as 1996, Sharma et al. encapsulated paclitaxel in liposomes made of phosphatidylcholine and
346 phosphatidylethanolamine to avoid Cremophore EL® utilization. Liposomes reached a higher
347 maximum tolerated dose of paclitaxel compare to Cremophore EL® formulation (Taxol®), but in
348 practice the best efficient dose was the same for both formulations. Authors did not show significant
349 difference in survival between liposomes and Taxol® after IP injection, maybe due to the cell line
350 chosen (P388 murine leukemia model) showing an intermediary sensibility to paclitaxel. However,
351 liposomes demonstrated a lower cumulative toxicity and the elimination of vehicle-mediated toxicity
352 as expected (Sharma et al., 1996).

353 At the beginning of 80's, Hirano et al. observed liposome in the lymphatic system. This process was
354 shown to be related to liposome size, in which small ones (50 nm) could easily reach the blood
355 circulation by thoracic lymph duct, whereas bigger ones (720 nm) were entrapped in lymph node
356 possibly aided by adhesion. Liposomes found into blood or lymph nodes were intact suggesting a
357 non-impaired drug release potential (Hirano and Hunt, 1985). Mirahamdi et al. also showed a better
358 retention in the peritoneal cavity for larger liposomes with a concentration 3 times higher for 1000
359 nm ones as compared to 100 nm, however liposomes measuring more than 1000 nm were less stable
360 and precipitated around abdominal organs. Liposome charge, lipid formulation, and PEG coating also
361 impacted the retention of liposomes in the peritoneal cavity. The negative charge of mesothelium
362 can indeed induce interactions with positively charged liposomes resulting in a prolonged residence
363 time in the peritoneal cavity. Moreover, PEG coating or lipid transition can impact the elimination of
364 liposomes, and therefore the residence of liposomes in the peritoneal cavity (Dadashzadeh et al.,
365 2010). Sadzuka et al. investigated the impact of lipid composition on the dissemination in peritoneal
366 cavity of doxorubicin encapsulated in liposomes. They did not show any relation between lipid
367 composition and clearance of doxorubicin from the peritoneal cavity, but once in the blood
368 circulation, doxorubicin plasma concentration from liposomes made of L- α -
369 distearoylphosphatidylcholine (DSPC) was superior to liposomes made of L- α -
370 dimyristoylphosphatidylcholine (DMPC). DSPC also allows a higher tumor penetration of liposomes
371 with a higher intratumoral doxorubicin concentration than DMPC after IP injection ($p < 0.001$)
372 probably due to a better stability of liposomes made with DSPC (Sadzuka et al., 2000). As mentioned
373 above, the particle size also affects the peritoneal cavity residence time. Bigger DSPC liposomes
374 around 4 μm remained in the peritoneal cavity after IP injection and disrupted to release doxorubicin
375 slowly. PEG addition in liposome formulation did not affect doxorubicin clearance from peritoneal
376 cavity neither liposomes absorption to the lymph and did not decrease large liposomes accumulation
377 in heart and liver. However, pegylation of small liposomes avoid accumulation in peripheral tissues (p

378 < 0,001) decreasing heart and liver toxicity and allowed a higher tumor penetration compared to
379 non-pegylated liposomes (Sadzuka et al., 1997). Authors also demonstrated that pegylation of
380 positively charged liposomes decreased doxorubicin concentration in peritoneal cavity while some
381 authors showed that PEG addition into neutral liposomes augmented their cavity retention
382 (Dadashzadeh et al., 2010).

383
384 Targeting was also proposed for liposomes. Liposomes encapsulating cisplatin, grafted with
385 transferrin (Tf) at the extremity of the were proposed (Yuda et al., 1996). Tf-PEG liposomes showed
386 higher survival rates ($p < 0.01$) and higher cisplatin levels in the peritoneal cavity as compared to PEG
387 liposomes without Tf and cisplatin in solution ($p > 0.01$), in a peritoneal dissemination model of
388 gastric cancer. The authors also confirmed by electronic microscopy the internalization of Tf-PEG
389 liposomes by a receptor mediated endocytosis process (Iinuma et al., 2002).

390
391 A new promising concept was developed consisting in thermosensitive liposomes. The goal of this
392 formulation was to inject liposomes IP and then induce a localized hyperthermia using high intensity
393 focused ultrasound reaching a maximum of 40°C allowing drug release from liposomes. This exciting
394 prospect still requires some improvements regarding the clinical application of hyperthermia
395 (Rezaeian et al., 2019).

396
397 For now, there are two doxorubicin liposomal formulations approved by FDA and EMA: Myocet®
398 which is a standard liposomal formulation and Doxil®/Caelyx®/Evacet®/Doxilen®/Lipodox® pegylated
399 formulations. To our knowledge no studies of Myocet® use in IP routes are available (clinical trial
400 consulted 24/10/2019). In contrast, Sugarbaker et al. just published an evaluation of Doxil®
401 administration by IP route for the treatment of PM after CRS. The first patient received 50 mg/m² of
402 Doxil® during 90 min in 2.55 L of 1.5 % dextrose heated at 41.5-43°C. At the end of the HIPEC, only
403 27% of drug penetrated the tissue surface of peritoneal cavity. The authors tried to prolong the
404 HIPEC duration to 180 min, increase Doxil® dose at 100 mg/m² and reduce the volume administered
405 to 2 L but drug uptake in tissues was not reproducible with a range of 22% to 60%. This HIPEC
406 optimization failure led authors to focus on early post-operative IP chemotherapy (EPIC). The
407 protocol consisted in mixture of t50 mg/m² Doxil® in 2 L of dextrose 1.5% instilled during 24 h. The
408 mean Doxil® absorption over 24 h was 85 ± 11% (Sugarbaker and Stuart, 2019). This result proved the
409 requirement of prolonged exposition of drug in peritoneal cavity to improve drug absorption into
410 peritoneum tissues. Further studied are needed to solidify the efficiency of Doxil® use in PM
411 treatment.

412

413 **3. Non particulate Drug Delivery Systems**

414

415 **3.1 Implants**

416 Thanks to their advantages allowing long term sustained release, reducing overall doses frequency of
417 administration and systemic side effects, facilitating patient compliance and enhancing their quality
418 of life, implants were considered by a few research teams to be transposable to PM. Li et al.
419 developed a 5-FU-loaded PLGA implant with a 1:1 ratio between the polymer and drug and various
420 molecular weight of PLGA to avoid an initial burst release In mice, middle (15 mg/kg) and high (22.5

421 mg/kg) dosages of 5-FU in implant of 1 mm diameter and 1 cm length showed significant tumor
422 inhibition compared to 5-FU solution ($p < 0.01$). Interestingly, 5-FU was mainly distributed in rectum,
423 small intestine, stomach and abdominal muscle with a lower amount in plasma (more than 50 times
424 less) (Li et al., 2018). Implant utilization was demonstrated to be safe with minimal off-target
425 toxicities recorded and with a better animal's tolerability compared to 5-FU solution.

426 However, several studies brought to light that PLGA-based implant developed a fibrous
427 encapsulation around the implant as a result of host inflammatory response (Athanasίου et al., 1996;
428 Ho et al., 2005). Ho et al., showed *in vitro* that increasing the size of implant associated with a higher
429 paclitaxel dose resulted in strongest inhibition of cell proliferation. No inflammation, infection or
430 distress neither encapsulation was observed *in vivo* 2 weeks after administration of chitosan and egg-
431 phosphatidylcholine implant (Ho et al., 2005). In contrast, implants made with other polymers as
432 polycaprolactone or poly(D,L-lactide) acid displayed fibrous encapsulation surrounding the implant
433 area. Drug release mechanism proposed by the authors was biphasic (Lim Soo et al., 2008). Indeed,
434 implant rapidly start to swell leading to the mobility of paclitaxel, followed by hydrolysis of chitosan.
435 Has a result, paclitaxel release was accelerated. *In vivo* studies highlighted several advantages of
436 implant use as compared to Taxol® solution: superior maximum tolerated dose, penetration in
437 tumor, antitumoral effect improved (Vassileva et al., 2007).

438 Despite these promising results, no clinical trial was performed and no clinical trial using implants
439 have been tested for peritoneal carcinoma. (clinicaltrials.gov)

440 **3.2 Smarts Hydrogels**

441 **3.2.1 Self-sustaining hydrogels**

442 Basically, hydrogels are mainly made of gelatin, pluronics, HA, chitosan, poly (organophosphazene),
443 caprolactone derivatives and are interesting for their rheological properties. Gelatin hydrogel granules
444 incorporating cisplatin was made by cross-linking an aqueous gelatin solution with glutaraldehyde.
445 Gel degradation accelerated when the amount of glutaraldehyde decreased. Granules obtained
446 presented irregular shapes with a size around 80-120 μm . *In vivo*, the proportion of collagenase
447 present in peritoneal cavity allowed a slow gel hydrolysis with 27 % degradation after 7 days and a
448 complete degradation within 3 weeks. Cisplatin granules hydrogel (10 mg/kg) induced less toxicity
449 than free cisplatin in solution (5 mg/kg), probably tanks to a lower passage of cisplatin in the blood
450 when administered in the hydrogel form. Antitumor efficacy was then assessed by the total photon
451 counts significant decreased in hydrogel-cisplatin group compared to the control group ($p < 0.05$)
452 which was in accordance with the survival rate that was prolonged in gel-cisplatin group compared to
453 control ($p < 0.05$) (Yamashita et al., 2019).

454 Smart hydrogels made with poly (organophosphazene) were also proposed to treat peritoneal
455 metastasis with gastric origin. Poly (organophosphazene) are inorganic polymers with a backbone
456 made of nitrogen and phosphorous atoms alternatively linked by single or double bonds. These
457 polymers are interesting thanks to their high variability in their functionalization. In that study,
458 hydrophilic and hydrophobic components such as isoleucine ethyl esters and α -amino- ω -methoxy-
459 PEG were grafted to prevent water/drug contact, and ensure water miscibility of the complex (Kang
460 et al., 2006). IP injection of hydrogel implemented with 15 mg/kg of PTX or one IP injection of PTX
461 solution at 30 mg/kg in mice intraperitoneally injected with HSC44 luc cells did not show significant
462 difference between hydrogel-PTX group and PTX solution group, but side effects like intestinal

463 dilatation and liver swelling were decreased in hydrogel-PTX group (Yu et al., 2012). Five years later,
464 the same team challenged approximately the same poly (organophosphazene) based
465 thermosensitive hydrogel mixed with 2 or 8 mg/kg of docetaxel (DTX). They compared the anti-
466 cancer drug effect of one injection of DTX-hydrogel at both DTX concentration and DTX solution
467 administrated IP or IV 2 times a week for 2 weeks at 2 mg/kg. They showed that a single injection of 8
468 mg/kg DTX-hydrogel reduced 4 times the tumor bioluminescence compared to IP DTX solution ($p =$
469 0.0001) after 28 days. The prolonged survival time observed in high dose DTX-hydrogel group
470 compared to IP DTX solution group ($p = 0.0068$) confirmed hydrogel capacity to suppress PM growth.
471 Another team chose to incorporate DTX in NP made of linoleic acid (CLA) and Pluronic F-127® to
472 enhance DTX solubility and control its release. At body temperature, the authors assumed that NP
473 turned into a hydrogel after IP injection, thanks to the thermoresponsive property of Pluronic® and
474 CLA. *In vitro*, DTX (10 mg/kg)-hydrogel enhanced cell apoptosis compared to DTX-solution (10 mg/kg)
475 alone with an apoptosis signaling overexpressed. In a PM model of mice injected IP with human
476 gastric cells, intra-abdominal uptake of ^{18}F -FDG was lower in the DTX-hydrogel group compared to
477 PBS and DTX-solution administrated IP ($p < 0.05$), which was consistent with the lower total number
478 of peritoneal nodules in DTX-hydrogel group ($p < 0.05$) associated with a prolonged survival (Bae et
479 al., 2013).

480 Polymers association is very common in thermosensitive hydrogel formulation. Wang's team studied
481 a triblock copolymer as follow: PEG methyl ether- ϵ -caprolactone-PEG methyl ether (PECE) 25 wt %.
482 Release study of 5-FU was done with 2 initial drug loading 0.5 mg and 1 mg. Both showed a burst
483 release during the first hour and reached a plateau after 3 days with respectively 95.3 % and 84.6 %
484 cumulative release. Moreover, a delayed release and increased uptake of methylene blue as a
485 marker of hydrogel was observed during 48h as compared to the methylene blue solution which was
486 discharged after 8h. PECE-5FU-hydrogel showed a smaller and decreased number of nodes compared
487 to 5-FU solution and control normal saline solution ($p < 0.05$), associated with an increased tumor
488 free rate and survival rate ($p < 0.01$ and $p < 0.05$ respectively) (Wang et al., 2010).

489 Our team also showed that the combination of poloxamer and alginate is efficient in PM treatment.
490 Association of P407, P188 and alginate (20/2/1 wt%) formed a non-toxic biocompatible thermogel
491 with a gelation temperature around 25°C. *In vitro*, the thermogel proved its ability to decrease cell
492 adhesion, a promising result to avoid post-surgical adhesions. *In vivo*, in a murine model of PM, the
493 thermogel loaded with both 5-FU and Oxaliplatin permitted to decrease significantly PCI score,
494 number of areas involved and mean ascites volume as compared to control group (respectively $p <$
495 0.005 ; $p < 0.05$ and $p < 0.001$). Further studies to evaluate thermogel distribution and adhesion in a
496 peritoneal cavity in an abrasion model of pig which is closer to the human peritoneal cavity volume
497 (Seguin et al., n.d.).

498 McKenzie et al. compared the efficacy of 3 drugs mixtures entrapped in PLGA-b-PEG-b-PLGA block
499 hydrogel (TheranoGel) or in PEG-b-PLA micelles measuring 190 nm (TheranoMic). They associated
500 paclitaxel with rapamycin, an mTor inhibitor known to potentiate sensitivity of certain cancer cells to
501 paclitaxel, and a near infrared optical imaging agent LS301. Slow Theranogel degradation kinetic
502 allowed a sustained simultaneous release of the 3 drugs *in vitro* as compared to TheranoMic ($p <$
503 0.0001). TheranoGel also showed debulking effect with a tumor burden decreased of 93 % within 3
504 days, whereas TheranoMic increased tumor burden (McKenzie et al., 2016).

505 Depani et al. developed a thermosensitive hydrogel based on a mixture of chitosan,
506 glycerophosphate as a cross-linker and 5-FU. The release of 5-FU out of the gel was quite fast with
507 40% after 1h and 75% after 12h. The anti-tumoral efficacy was evaluated after a five injections series
508 within 17 days. No difference was found in tumor volume between 5-FU solution group and 5-FU-
509 hydrogel group, but lower systemic toxicity was observed with less morbidity and mortality in 5-FU-
510 hydrogel group demonstrating interest of such formulations compared to drug in solution with
511 systemic exposure (Depani et al., 2013).

512 Chen *et al.* combined chitosan and HA to an intelligent biopolymer system, poly(N-
513 isopropylacrylamide) (PNIPAM) able to exhibit reversible solution-to-gel phase transition behavior.
514 Drug release was biphasic with a burst of 40% in 8h due to fast diffusion of Doxorubicin through
515 pores due to its low molecular weight, and a prolonged phase due to gel degradation reaching 80%
516 after 12 days. *In vivo* studies revealed a lower number of tumors with smaller weight and volume in
517 Dox-hydrogel group compared to Dox-solution group indicating a better suppressing tumor growth
518 effect ($p < 0.05$). Anti-adhesion effect was also assessed on a sidewall defect cecum abrasion animal
519 model. Histology showed a better adhesion score in Dox-hydrogel group compared to Doxorubicin
520 solution and control group ($p < 0.001$). Authors concluded that hydrogel improved Doxorubicin effect
521 by sustained release and extend lifespan of mice with an anti-adhesion effect thanks to its barrier
522 effect until healing to prevent peritoneal adhesion (Chen et al., 2018).

523 Emoto *et al.* choose to design a thermosensitive hydrogel based on HA derivatives loaded with
524 cisplatin to treat peritoneal dissemination of gastric cancer. HA was modified to obtain one
525 aldehyde form (HA-CHO) solution and one adipic dihydrazide (HA-ADH) solution separately. Solutions
526 merged together in a single needle at the time of administration in peritoneal cavity and gelation
527 occurred *in situ* in 40 sec. Cisplatin release was prolonged over 4 days with a cumulative release
528 around 80%. After mice IP treatment once a week for 3 weeks with 1 mg/kg cisplatin for all groups,
529 the antitumor activity was better achieved in gel-cisplatin group compared with cisplatin solution
530 group ($p = 0.032$) which results were not different from PBS control group (Emoto et al., 2014).

531 3.2.2 Hydrogels with DDS incorporated inside

532 In this last part, we referenced studies associating drug delivery systems into thermosensitive
533 hydrogels to improve sustained release and containment of drug in peritoneal cavity. The solution
534 state of hydrogel prior to use allowed incorporation of DDS as a suspension. *In situ* gelation led to
535 cover the peritoneal cavity keeping particles of drugs in place to have a cytotoxic local effect.

536 Several teams chose to work with HA-ADH and HA-CHO network.

537 Ohta's team used the combination of HA-ADH and HA-CHO as a hydrogel matrix in which they
538 inserted a nanogel of HA loaded with cisplatin to treat a mouse model of gastric cancer with
539 peritoneal dissemination. They compared iminodiacetic acid (IDA) or malonic acid (MA) as chelating
540 ligand conjugated to the HA backbone to attach cisplatin, and the load method of cisplatin-nanogel in
541 HA matrix with a physical encapsulation or a chemical conjugation. The release of cisplatin out of HA
542 matrix and HA nanogel polymer was quite inferior in chemical conjugation formulation and MA group
543 after 1 week. The total number of peritoneal nodules was significantly lower in group treated with
544 IDA-nanogel physically encapsulated in HA matrix compared to cisplatin in solution ($p = 0.032$).

545 Authors also brought to light the enhance therapeutic effect on nodules < 1 mm, results explained by
546 a limited tumor penetration of nanogels in bigger nodules (Ohta et al., 2017).

547 Bajaj *et al.* compared the anti-tumoral activity of two DDS in HA based hydrogel, the first one was
548 nanoparticles of Taxol[®] in its commercial form *ie.* in Cremophor EL[®] micelles around 14 nm (NP-PTX),
549 the other was a suspension of microparticulate PTX precipitates (MP-PTX) around 100 μm. Both
550 solutions contained 0.69 mg/mL of paclitaxel and rapidly formed a gel upon administration stayinc
551 peritoneal cavity until 2 weeks. The NP-PTX-gel showed a cumulative release of 15.6% in the first 24h
552 followed by no further release, whereas the MP-PTX-gel reached progressively 38.5% after 10 days.
553 This observation matched with the amount of PTX found in peritoneal fluids which was superior with
554 MP than NP at day 14, with respectively 0.9-5.1 μg/mL and 0.02-0.94 μg/mL, confirming the interest
555 of larger particles size to remain in peritoneal cavity. However, the anti-tumor efficacy assessment
556 did not show a statistical difference between gel groups and Taxol[®] solution group (Bajaj et al., 2012).

557 To overcome the size particles problem, authors tried to replace PTX aggregates by PTX nanocrystals
558 produced by breaking down large particles or crystallizing drug solution measuring around 258 nm.
559 The *in vitro* paclitaxel retention in SKOV3 was enhanced with PTX nanocrystals compared to PTX
560 aggregates. The *in vivo* anti-tumor activity was evaluated in mice after one single administration of
561 treatment IP with an equivalent of 30 mg/kg of PTX. The survival of mice receiving PTX nanocrystals-
562 gel was significantly prolonged as compared to Taxol[®] solution group and MP-PTX-gel (p < 0.005).
563 However, bioluminescence observation of SKOV3-luc cells showed a minimal tumor burden growth in
564 PTX nanocrystals-gel group up to 7 weeks after treatment. This study point to the beneficial effect of
565 particle size reduction, which lead to a greater dissolution rate and cellular uptake of PTX (Sun et al.,
566 2016).

567 In a subsequent work, the same team encapsulated cisplatin in NP of HA measuring 270 nm. The
568 entrapment of cisplatin-NP in gel did not impact kinetic of cisplatin release irrespectively of the gel
569 concentration (20 or 40 mg/mL of HA). The hyaluronic gel was still present after 2 and 4 weeks of
570 treatment in peritoneal cavity but no cisplatin was collected in lavages indicating a full release of the
571 drug out of the gel in less than 2 weeks. The authors observed by confocal microscopy a decrease in
572 cellular uptake of cisplatin in SKOV3 cells in presence of HA in excess in the medium culture. This
573 competition between HA-NP based and free HA suggests that NP entered cells via HA receptors as
574 CD44, which are known to be overexpressed on the surface of ovarian cancer cells providing a
575 selective cytotoxic effect (Li and Howell, 2010, p. 44; Zagorianakou et al., 2004, p. 44). Unfortunately,
576 the antitumor effect study did not show any superiority of the cisplatin-NP gel compared to the
577 cisplatin solution even with a total dose of cisplatin in NP superior to the maximum tolerated dose. A
578 later increase in tumor burden suggests potential involvement of empty carriers and degradation
579 products in the growth of residual tumors which can alert on HA use (Cho et al., 2015).

580 Fan *et al.* associated PLA and Pluronic[®] to build NPs co-loaded with DTX and LL37, an endogenous
581 tumor-suppressing peptide, to benefit from synergistic effect on cell viability and apoptogenic
582 effects. PLA-(Pluronic L35)-PLA block copolymers-based NPs measured around 129 nm and were
583 monodisperse. Hydrogel made with PLA-(Pluronic L64)-PLA triblock copolymer showed a porous
584 tridimensional structure with homogenous micropores size permitting diffusion of NPs. Hydrogel
585 allowed a slower release of DTX as compared to NPs (p < 0.005). *In vivo* antitumor activity of DTX-

586 LL37-NPs hydrogel attested an important decrease of number and weight of tumor nodules in
587 peritoneal cavity at day 30 after a single IP injection ($p < 0.01$) with a smaller size of nodes compared
588 to other groups. This finding was in accordance with a median survival time increased significantly in
589 DTX-LL37-NPs hydrogel group compared to control ($p < 0.01$) (Zhou et al., 2015).

590 Another team worked on Pluronic[®] based hydrogel loaded with a combination of drugs enclosed in
591 NPs. PLA added with Pluronic[®] 10R5 formed NPs in which oxaliplatin (OX) and tannic acid (TA) were
592 loaded, measuring between 143 and 163 nm depending on drug/polymer ratios. The hydrogel was
593 composed by ϵ -caprolactone and Pluronic[®] 10R5 as block copolymer resulting in a porous three-
594 dimensional structure remaining detectable in peritoneal cavity up to 10 days. The release of OX was
595 considerably increased when NPs were not embedded within the gel with a cumulative rate around
596 65 %, which is in favor of a delaying effect of the gel. The *in vivo* antitumor activity assay revealed a
597 significant decreased in number, size and weight of tumor nodules with OX/TA NPs hydrogel group
598 compared to control, free OX and OX NPs groups ($p < 0,05$), in accordance with the prolonged
599 median survival time in OX/TA NPs hydrogel group ($p < 0.05$). Tissue sections also showed an
600 increased number of apoptotic cells, a tumor cell proliferation suppression and a lower micro vessels
601 density in OX/TA NPs hydrogel group compared to other groups which is in favor of a better
602 antitumoral activity (Ren et al., 2019).

603 Yun *et al.* designed a bicompartamental system to deliver two cytotoxic components. Firstly, they
604 encapsulated 5-FU in biodegradable poly- (ϵ - caprolactone)-poly (ethylene glycol)-poly(ϵ -
605 caprolactone) (PCL-PEG-PCL, (PCEC)) copolymers micelles. Then, they mixed the micelles with a
606 chitosan solution crosslinked with β -glycerophosphate and loaded with cisplatin to obtain a
607 thermosensitive hydrogel. The authors also compared the release profiles of 5-FU and cisplatin drugs
608 out of the gel and highlighted an important difference between both drugs with 85 % and 40 %
609 cumulative release respectively in 144h. *In vivo*, the number of tumor and their weight were
610 significantly lower in 5-FU micelles-cisplatin gel group compared to free 5-FU/cisplatin ($p < 0.05$) and
611 control group ($p < 0.001$) in accordance with a prolonged survival time. The absence of liver and lung
612 metastasis in 5-FU micelles-cisplatin gel group was in accordance with the high decrease of
613 proliferation level evidenced by the Ki 67 positive cells number (Yun et al., 2017).

614 PCEC block copolymers was also chosen by Gong et al. to form 21 nm PTX-micelles and 5-FU hydrogel
615 depending on the molecular weight of PCEC. Release of 5-FU and PTX was assessed through the
616 whole micelle-gel system. Authors highlighted a difference in release kinetic between 5-FU and PTX
617 at day 10, respectively 90% and 30%, explained by hydrophobicity of PTX which had strong
618 interaction with PCEC inducing a lower drug release rate whereas high solubility of 5-FU allowed its
619 diffusion through hydrogel pores more rapidly. *In vivo* pharmacokinetic investigation showed AUC_{0-24}
620 and $t_{1/2}$ superior in PTX-micelles-5-FU-gel group compared to free Taxol[®] and 5-FU in solution group
621 leading to a much higher 5-FU and PTX concentration in the abdominal cavity ($p < 0.001$). A minimal
622 increase of tumor weight and number was observed in mice receiving PTX-micelles-5-FU-gel after
623 one IP injection compared to control and Taxol[®] + 5-FU solution. These finding was in accordance
624 with increase in the life span observed in PTX-micelles-5-FU-gel group (Gong et al., 2012a).

625 Another team formulated a “two in one” drug delivery system made of NPs formulated with
626 biodegradable copolymer associating polyester and polyethylene glycol, forming gel after

627 reconstitution in water. In a previous study, the amphiphilic triblock copolymer poly(e-caprolactone-
628 co-1,4,8-trioxa [4.6]spiro-9-undecanone)- poly(ethyleneglycol)-poly(e-caprolactone-co-1,4,8-trioxa
629 [4.6] spiro-9-undecanone) (PECT) demonstrated a safety of use in mice and formed spherical NPs
630 around 209 nm entrapping PTX after redispersion in water. The cumulative release of NPs-PTX based
631 PECT hydrogel was around 53 % at day 46 with a 2.5 mg/mL concentration of PTX (Wang et al.,
632 2013). In the present study, authors studied the NPs-PTX-PECT hydrogel behavior after IP injection.
633 They identified a modest histological inflammation during the first 3 days disappearing on day 5
634 which was linked to the concomitant hydrogel degradation. Fluorescence signal demonstrated a
635 major localization of the gel in intestines until day 8, which is in accordance with the absence of
636 toxicity in other organs. The *in vivo* anti-tumor efficacy was assessed after single IP injection
637 treatment of NPs-PTX-PECT hydrogel with 30 mg/kg of PTX. On day 11, weight of tumor nodules was
638 significantly lower as compared to Taxol[®] in solution group which administration schedule was 3
639 injections in a week each dosed with 10mg/kg of PTX ($p < 0.05$). However, decreased in tumor
640 burden stilled important compared to control group at the end point ($p < 0.01$) despite of a tumor
641 cells regrow in all groups. In the first 96h, pharmacokinetic study revealed higher AUC and $t_{1/2}$ in NPs-
642 PTX-PECT hydrogel compared to Taxol[®] group ($p < 0.001$) which can explain the enhance therapeutic
643 effect in peritoneal cavity maintaining high PTX concentration near tumor nodules for a prolonged
644 period (Xu et al., 2016).

645 4. Conclusive prospects

646

647 Patients with peritoneal metastasis have a poor prognosis and a median survival reduced compared
648 to other sites of metastasis (Franko et al., 2012; Guimbaud et al., 2014). The conventional approach
649 consisted of a 5-FU based systemic chemotherapy but was associated with poor survival outcome of
650 approximatively 6 months (Klaver et al., 2012). Since 2003, the standard of care of peritoneal
651 metastasis combined cytoreductive surgery with HIPEC but an important relapse rate still observed
652 (Bijelic et al., 2007; Verwaal et al., 2004). There is an important challenge to develop efficient
653 therapeutic innovations to prevent peritoneal metastasis implantation and to treat it if already
654 present.

716 This area of research attracted many teams since several years and various chemotherapies and
717 carrier were tested to offer surgeons an easy to use solution to treat suspicious carcinomatosis. The
718 ideal DDS for IP therapy might regroup several characteristics such as biocompatibility, high drug
719 concentration in peritoneal cavity maintained for a prolonged period of several days, tumor
720 specificity, low local and systemic toxicity and efficient tumor penetration. We reviewed here most of
721 strategies used to treat peritoneal metastasis from digestive or ovarian origin. We delimited 3
722 different DDS strategies.

723 The first one consisted of particulates DDS, we identified five kinds of particles: microparticles,
724 nanoparticles, micelles, polymersomes and liposomes. Basically, quite a few messages came out like
725 drug release depends on particles size, smaller are the particles better is the distribution inside the
726 peritoneal cavity but higher is the risk to accumulate in lymph nodes or spleen. The task is to
727 consider the benefit/risk balance of each kind of particles to avoid side effects like local inflammation
728 and adhesion observed in some cases with microparticles, or systemic passage with micelles for

729 example. A meticulous choice of polymers is also essential to ensure its biocompatibility and to
730 resolve certain problematics like adhesion. In addition, DDS formulated with component targeting
731 cancer cells seems to be promising. In our point of view, we believe that microparticles are especially
732 interesting because their size could avoid leakage through subdiaphragmatic pores and lymph nodes
733 allowing a prolonged residence time in peritoneal cavity thus increasing contact of nodules with drug
734 with a limited systemic toxicity.

735 The second strategy used non particulates drug delivery systems including implants, films and gels.
736 Films were mainly described for their anti-adhesion property by a mechanical action (Uguralp et al.,
737 2008)(Paulo et al., 2009)(Mamoudieh et al., 2011). When loaded with drugs the goal of
738 pharmaceutical action was also to prevent post-surgical adhesions but were rarely used as DDS to
739 treat peritoneal metastasis. Implants represent an interesting approach in metastasis care because it
740 can be fixed near tumor site with an important dose of drugs inserted inside protected by a polymer
741 barrier allowing a controlled release with a zero-order kinetic. But for a peritoneal cavity, it is limited
742 to a specific place. For that, implant had to be considered as DDS more as a solution to decrease a
743 local relapse for no margin resection surgery, than for peritoneal metastasis (Baitukha et al., 2019).
744 In contrast, gel can cover the whole peritoneum surface. The main challenge consists in the
745 obtention of a homogenous repartition of the drug with a limited inserted volume, which could be
746 better obtained thanks to a gel with rheofluidifiant behavior. This aspect was not widely described. In
747 a recent work, our team studied *in vitro* and *in vivo* characteristics of such a gel based with a
748 combination of poloxamer and alginate highlighting its anti-tumor and anti-adhesion effects (Seguin
749 et al., n.d.).

750 The last strategy combined aspects of the two previous ones meaning gels loaded with particles. This
751 option represents many advantages. Gel allows repartition all over the peritoneum wall and remains
752 in place for a prolonged period, thus particles are localized near to nodules and can operate a local
753 release of cytotoxic agents contained inside. Drug liberation is dependent of gel and particles such as
754 diffusion or degradation often resulting in a sustained release in comparison to particles alone. This
755 strategy appears to be the most promising thanks to combination of two compartmentation
756 advantages.

757 It is important to mention that storage condition needs to be practical and easy, because part of the
758 surgery could be performed in an emergency situation. The surgeon discovers a situation with a high
759 peritoneal metastatic risk and had to offer a solution, without any pre-operative strategy. A storage
760 solution for the DDS had to be simple, easy access and every time during the day and night. By
761 example, a complex DDS using an instable drug needing a complex storage condition or a DDS drugs
762 complex that had to be built in the pharmaceutic unit one hour before could not be a good solution.

824 To our knowledge, there is no human clinical trial yet assessing efficacy of drug delivering systems to
825 treat or prevent peritoneal metastasis. Current clinical trials focus on HIPEC or pressurized intra
826 peritoneal aerosol chemotherapy (PIPAC) ameliorationBased on promising results obtained with
827 animal models, drug delivery systems listed above might represent an interesting tool being less time
828 consuming and safer for surgerons than HIPEC and PIPAC, and not requiring any additional
829 machinery.

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1173

1174 **Figure 1:** (A) Two layers of peritoneum cover the abdomen: the parietal layer lines the abdominal
1175 wall, while the visceral layer lines the abdominal viscera. The narrow space within these two layers is
1176 referred to as the peritoneal cavity. (B) The layer of mesothelial cells is referred to as the peritoneum
1177 and, collectively, the connective tissue and peritoneum are referred to as the serosa. The serosa is
1178 situated directly beneath the abdominal musculature. Reprinted from Capobianco *et al.* 2017 with
1179 permission.

1180 **Figure 2:** Schematic representation of the main lymphatic absorption pathways for macromolecules
1181 after IP administration. Reprinted from Al Shoyaib *et al.* 2020 with permission (Tsai *et al.*, 2007).

1182 **Figure 3:** Drug distribution in the peritoneal cavity after IP injection of paclitaxel (10mg/kg)
1183 depending of formulation: paclitaxel solubilized in Cremophor EL/ethanol (*empty square*), paclitaxel-
1184 loaded gelatin nanoparticles (*filled triangle*) and paclitaxel-loaded polymeric microparticle (*filled*
1185 *circle*). A control group of mice received paclitaxel solubilized in Cremophor EL/ethanol intravenously
1186 (filled diamond) (a). Paclitaxel concentration-time profiles in peritoneal cavity (b) and in plasma (c).
1187 * $p < 0.001$. Reprinted from Tsai *et al.* 2007 with permission (Tsai *et al.*, 2007).

1188 **Table 1:** Microparticle data summarized.

1189 **Table 2:** Nanoparticle data summarized.

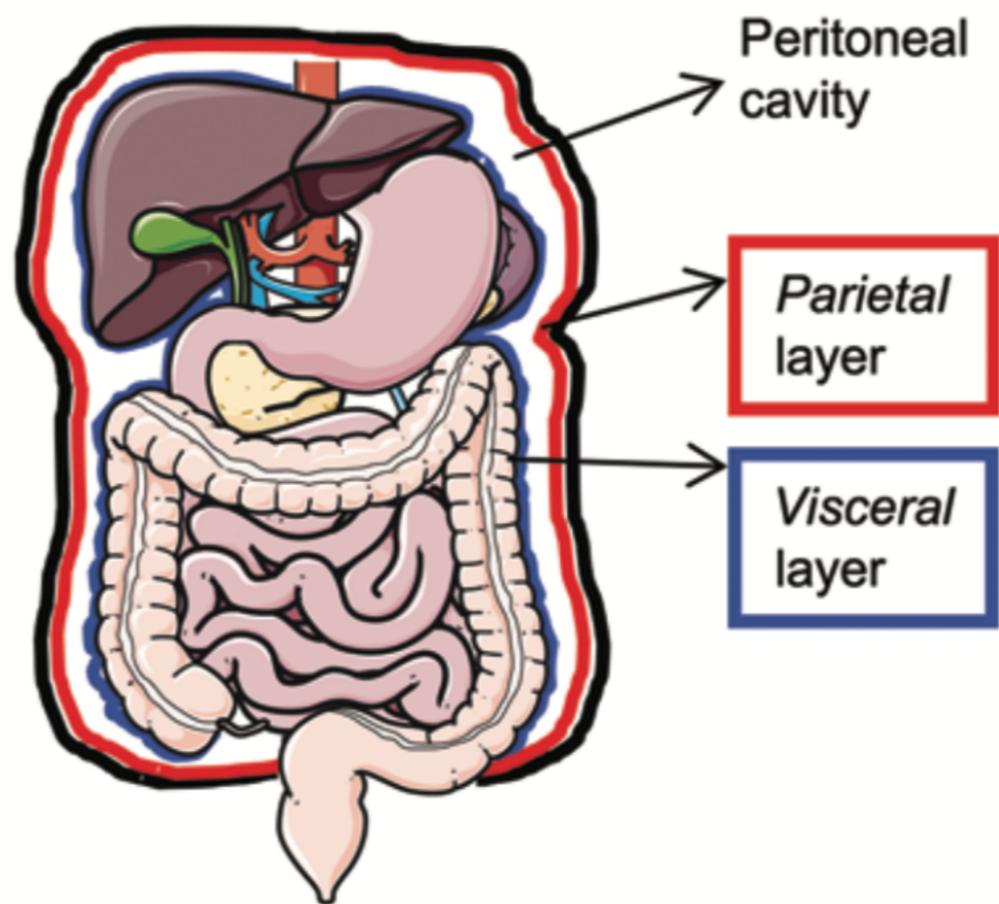
1190 **Table 3:** Advantage and inconvenient of each drug delivery system

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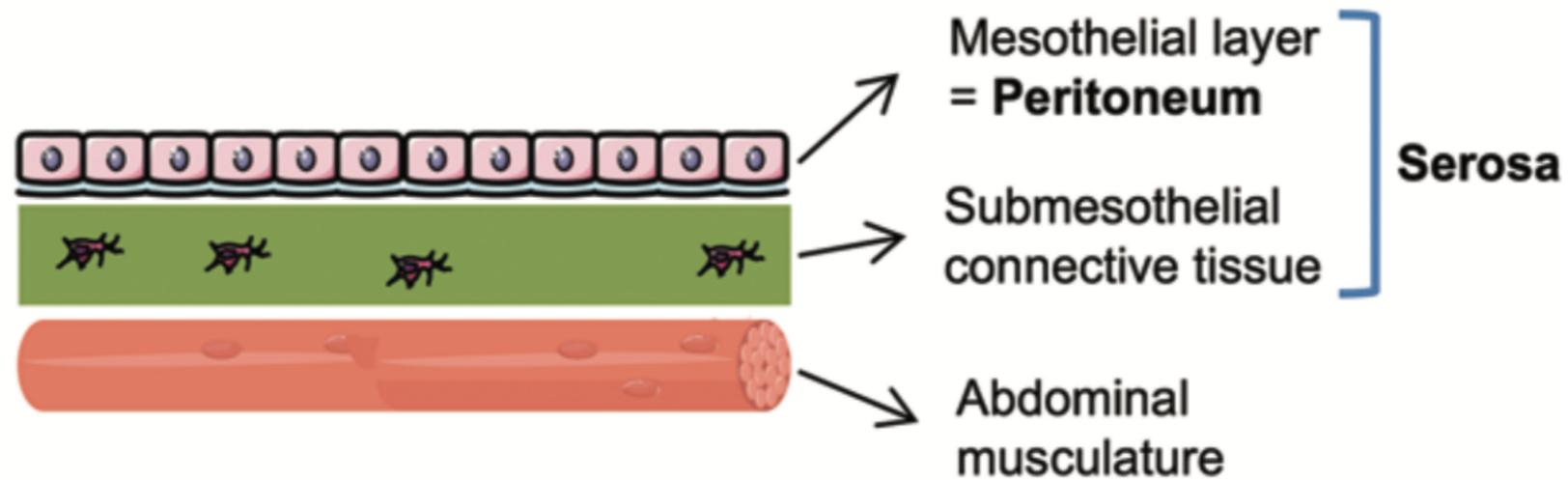
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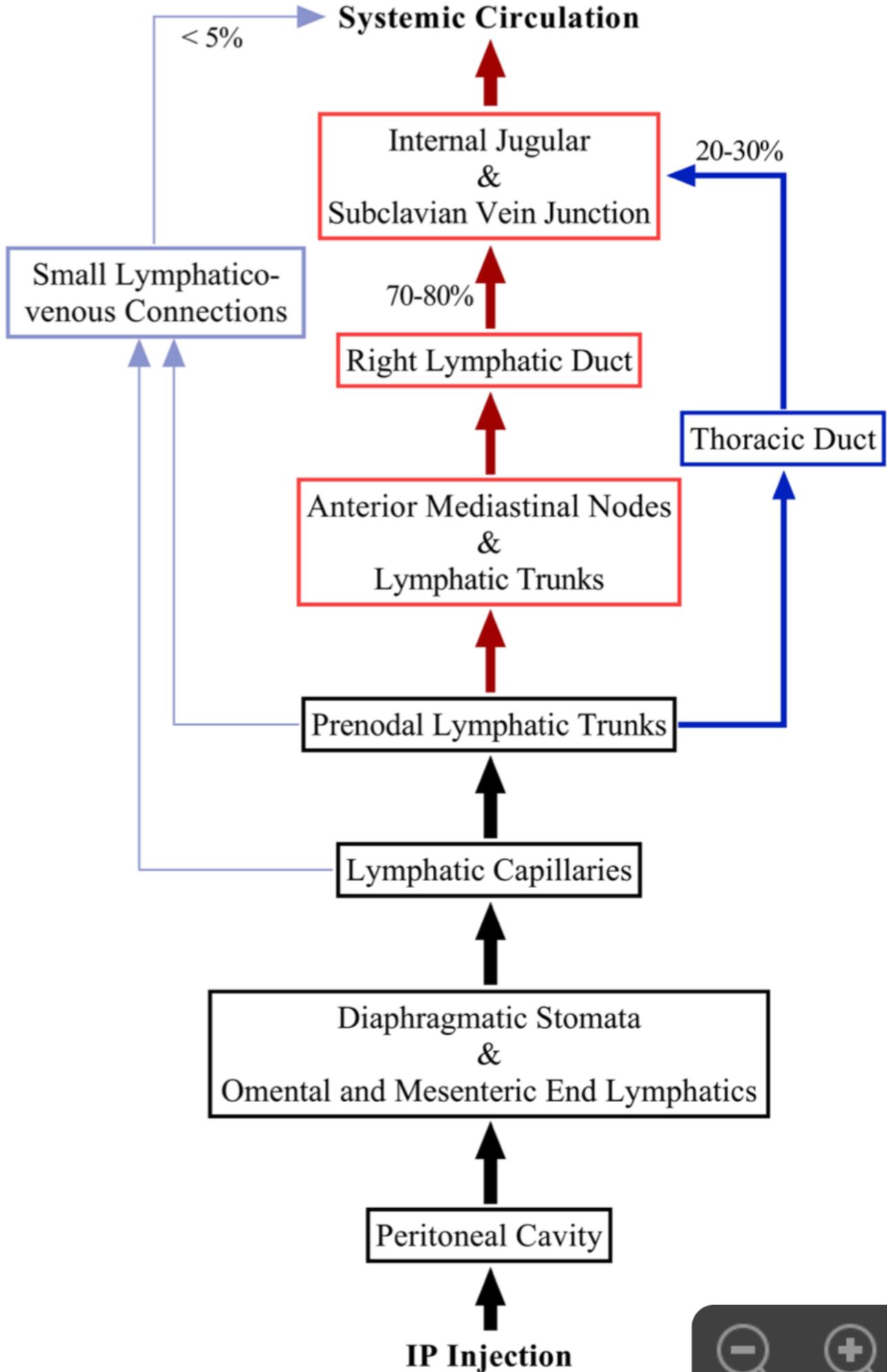
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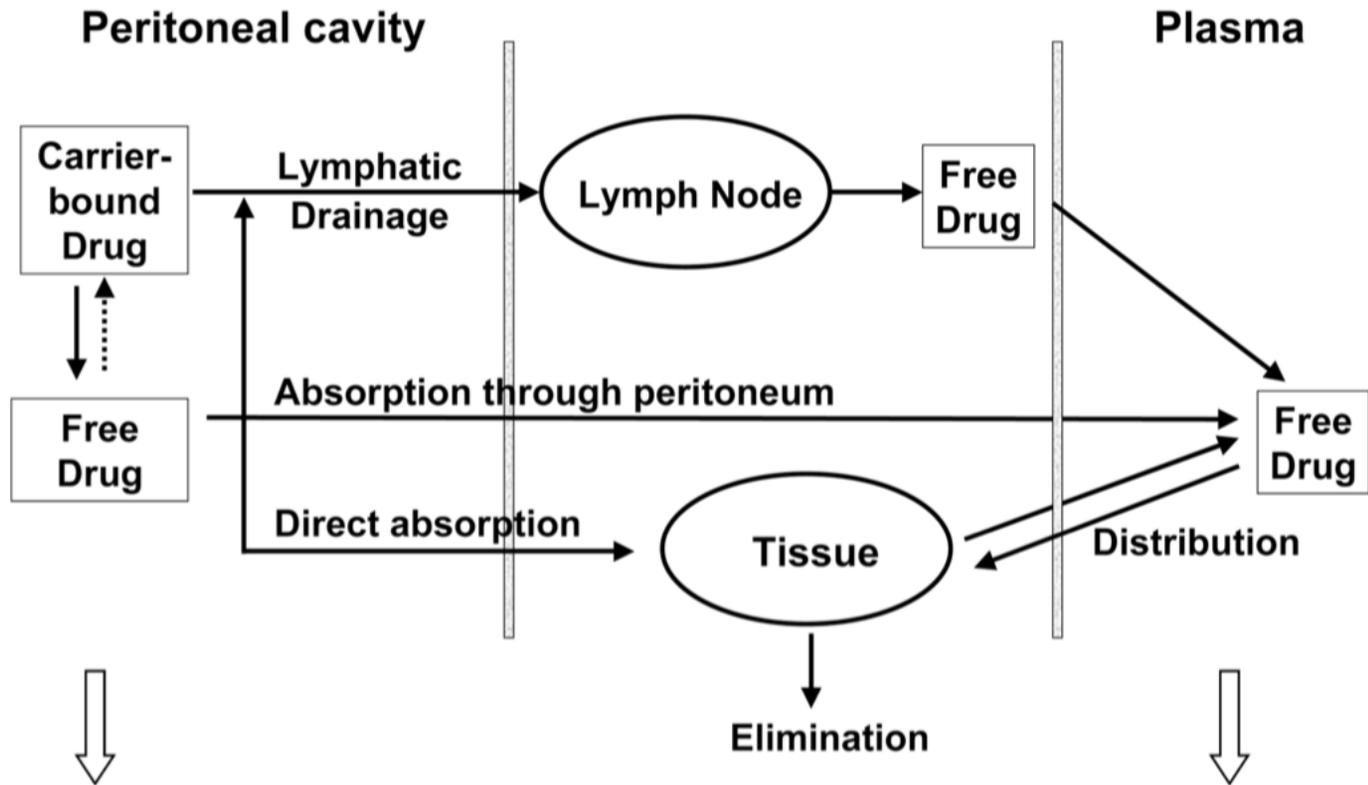


B

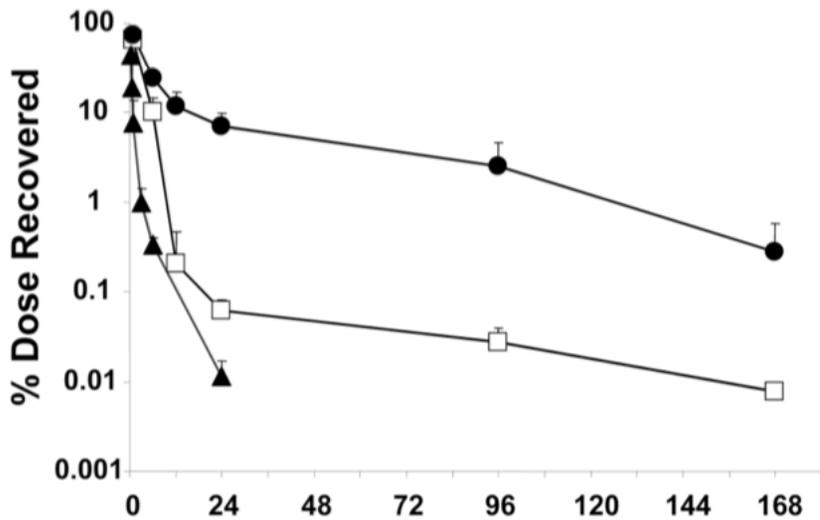




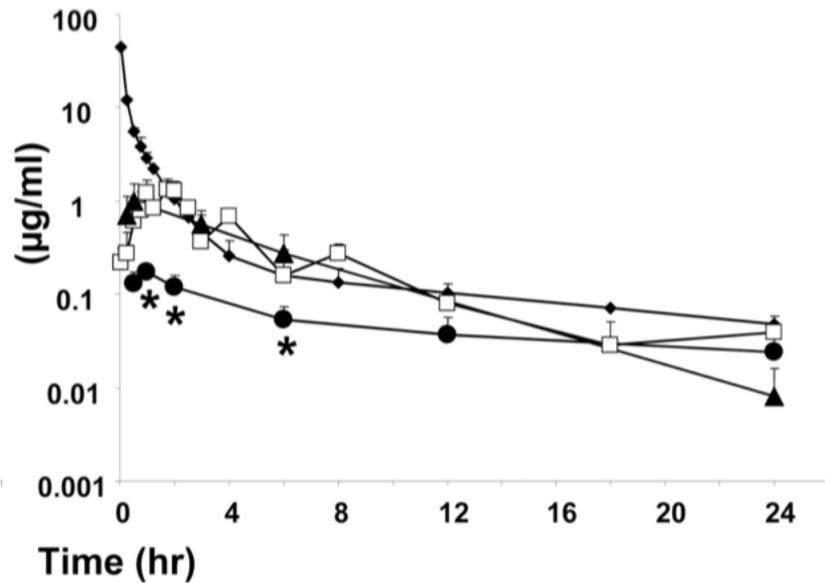
A. Disposition of IP Therapy



B. Profiles in peritoneal cavity



C. Profiles in plasma



Ref	Drug delivery system	Release	Tumor lines	Animal model / Treatment groups	Results
De Clercq 2019	- Gelatin - Genipin - Paclitaxel	24h : 7% Day 14 : 19 to 60%	SKOV3 2x10 ⁶	Femal BALB/C nu mice - MS of paclitaxel as solution - MS of paclitaxel as nanosuspension of nanocrystals -Abraxane®	PTX-treatment IP significantly improved survival of mice in a microscopic peritoneal carcinomatosis mouse mode. MS of paclitaxel as nanosuspension was the only group showing significantly decreased PCI score and decreased of ascites compared to both control groups. The optimal dose of MS of paclitaxel as nanosuspension was ranged from 7.5 to 15 mg PTX/kg.
Fan 2014	- Poly(L-lactic acid) - Pluronic L121 - Docetaxel Drug loading : 7% Diameter : 45µm	24h: 17% Day 8: 60%	CT26 2x10 ⁵	Male BALB/C mice - Docetaxel-MS 8mg of docetaxel/kg once a week - Docetaxel solution 4mg/kg 2 times a week	Tumor node numbers and size and the Ki-67 from docetaxel-MS group were significantly less than other groups. The median survival in docetaxel-MS group was significantly longer compared with docetaxel solution (p < 0.05).
Gunji 2013	- Gelatine - Cisplatin		Colon-26 1x10 ⁶	Male BALB/C mice - Cisplatin-MS (10mg cisplatin/kg) - Cisplatin solution (10mg cisplatin/kg)	No difference in the tumor weight was detected between the cisplatin-MS and free cisplatin solution groups. Cisplatin-MS showed a prolonged survival time compared with cisplatin solution (p < 0.05).
Lu 2008	- Poly(DL-lactide-coglycolide) - Paclitaxel Drug loading : 4.1+-0.5% Diameter : 4µm	24h: 70% and then 1% daily	Human ovarian SKOV3 2x10 ⁷	Femal athymic BALB/c Nu/Nu mice - MP: 40 or 120 mg/kg - Paclitaxel/ Cremophor EL 4x10 mg/kg or 8 x15 mg/kg	MP showed higher concentrations and deeper penetration compared with the group treated with the Cremophor EL carrier.
Tsai 2007	- Poly(D,L-lactide-co-glycolide) - Paclitaxel Drug loading : 3,77% Diameter: 5,77µm	about 70% in 24 h under sink conditio ns	Hs766T 20x10 ⁶	Female nude Balb/C mice - Paclitaxel-loaded Cremophor micelles, - Paclitaxel nanoparticles, - Paclitaxel microparticles (paclitaxel-equivalent dose of 40 mg/kg for all three formulations)	Microparticles, which had the slowest drug release, yielded the lowest rate and extent of systemic absorption in the first 24 h. Microparticules increased significantly greater the medium survival rate compared to other treatment group.
Armstrong 2006	- Lactide - Propylene glycol - Ethyl phosphate - Paclitaxel (=Paclimer®) Drug loading : 10%			Human with recurrent or persistant ovarian or primary peritoneal carcinoma Paclimer® starting was 60 mg/m ² IP every 8 weeks for two cycles	3 out of 13 patients were progression free for at least 6 months after completing therapy. Marked inflammatory response (adhesions, necrosis and fibrous connective tissue and foreign body giant cell reaction with residual polymer filaments) was observed in 1 patient and was supposed to be due to polymer.
Kohan 2006	- Poly-(lactic-co-glycolic) acid (PLGA) Diameter : 5-25-60µm			Male SV129 mice - carrier fluid containing MP	MP made from lower Mw polymers had much lower incidences on adhesion.

Liggins 2000	- Poly(L-lactic acid) - Paclitaxel 30% (w/w) Drug loading : 97% Diameter : 30- 120µm	24h: 4% Day 30: 25%	9-L glioblast oma 2x10 ⁶	Mal Wistar rats - 100mg MS	No tumors or tumor nodules or ascites were visible in the peritoneal cavities of any rats which received paclitaxel loaded MS after either 2 or 6 weeks. All animals in control group died before 4 weeks.
Tokuda 1998	- Poly-d,l-lactic acid (PLA) - Polyethylene glycol acid 10% - Cisplatin Diameter : 223µm	24h: 14%, Day 30: 85%	Yoshida sarcoma 6x10 ⁶	Male Donryu strain rats - Cisplatin-MS (8-12- 16mg/kg of cisplatin) - Cisplatin solution (8mg/kg of cisplatin)	In the cisplatin-MS group, the number of peritoneal metastasis was more decreased with the smallest dose of cisplatin. The survival time of rats was significantly better with high doses of cisplatin.
Hagiwara 1996	- Poly (glycolide-co- lactide) - 5-FU Diameter : 24µm		B-16 melanom a 1x10 ⁶	Male BDF1 mice - 5-FU-MS (100-150- 200-300-400mg/kg) - 5-FU aqueous solution (100-150- 200mg/kg)	Survival time was significantly prolonged with 5-FU-MS compared to 5-FU solution at the same dose with a reduced systemic toxicity.
Kumagai 1996	- L-lactic acid and glycolic acid copolymer (PLGA) - Cisplatin Drug loading : 5% Diameter : 100µm	Slow during 3 weeks	DMBA induced ovarian cancers 1x10 ⁷	Female Wistar rats - Cisplatin-PLGA (2,4- 4,8-7,2mg/kg) - Cisplatin solution 2,4mg/kg	Cisplatin-PLGA group showed a greater increase in their mean survival time compared with cisplatin solution group. This increase is proportional to cisplatin dosage.
Takahashi 1995	- Activated charcoal - Mitomycin Diameter : <40µm			Human undergoing gastrectomy for gastric carcinoma with serosal infiltration grade S2 or S3. -Mitomycin-MP IP 50mg	Overall survival was greater in Mitomycin-MP group at 1,5-2-2,5 ad 3 years for patient without macroscopically defined peritoneal carcinomatosis.
Hagiwara 1992	- Poly d,l-lactide - Cisplatin Diameter : 50- 150µm	24h: 40- 50% Day 20: 20-30%	Mouse ovarian histiocyti c sarcoma (M5076) 1x10 ⁶	Male BDF1 mice -Cisplatin-MS(1-2,5- 5-10-25mg cisplatin/kg) -Cisplatin solution (1- 2,5-5-10-25mg cisplatin/kg)	At equivalent doses in toxicity a significantly greater number of mice survived with cisplatin-MS treatment compared with with cisplatin-solution treatment (p<0,001).

Table 1: Microparticle data summarized.

Ref	Drug delivery system	Tumor lines	Animal model / Treatment groups	Results
Coccolini 2017	- Albumine - Paclitaxel (=Abraxane®)		Female New Zealand White Rabbits -Abraxane 10.83mg/kg - Paclitaxel Cremophor-EL 10.83mg/kg	Paclitaxel penetration in abdominal wall of the rabbits treated with nab-paclitaxel was significantly higher than paclitaxel in solution (p=0.0002).
Gilmore 2013	- Methacrylate monomer - Paclitaxel	OVCAR-3 10 ⁶	Femal (Nu/J) mice - Paclitaxel expansive NP 10mg/kg - Paclitaxel Cremophor-EL 10mg/kg	Expansile NP swelling appears to delay or prevent their exocytosis from tumor cells. Expansile NP demonstrated their ability to accumulate in areas of tumor. No recurrence was observed in eNP group compared with 43% in paclitaxel cremophor-EL group.
De Smet 2012	- Pluronic F127 - Pluronic F68 -Paclitaxel Diameter: 400nm	SKOV-3 30x10 ⁶	Adult female athymic nude rats -Nanocrystalline paclitaxel formulation - Taxol®	No significant differences were observed on tumor growth between both PTX formulations at day 7 and 14 after HIPEC tratment
Werner 2011	- Poly (lactic-co-glycolic acid) (PLGA) - Lecithin - Distearoyl phosphoethanolamine-PEG-COOH - Folate - Paclitaxel - Yttrium ⁹⁰ Diameter: 75+/- 10nm	SKOV-3 14x10 ⁶	Female Nu/Nu mice - folate-targeted NP 20 µg Paclitaxel and/or 50 µCi of Yttrium-90 - non-targeted NPs 20 µg Paclitaxel and/or 50 µCi of Yttrium-90	Mice receiving folate-targeted nanoparticles had significantly longer survival than mice that received non-targeted nanoparticles (p=0.01). No statistical significance when comparing NPs containing both chemotherapy and radiotherapy to either therapeutic alone.
Colson 2011	- Acrylate based polymer - 2,4,6-trimethoxybenzaldehyde - Paclitaxel Diameter : 100nm at physiological pH and 1000nm at acidic pH	Human malignant pleural mesothelioma cell lines MSTO-211H 5x10 ⁶	Female athymic nude (Nu/J) mice - Paclitaxel expansile NP - Paclitaxel Non expansile NP - Paclitaxel solution	Paclitaxel expansile NP in vivo was associated with slower drug release kinetics, prolonged intracellular accumulation of paclitaxel and a marked affinity of the NP for sites of local tumor in situ that persists for at least several days after injection. Survival was significantly superior in paclitaxel expansile NP group.
Kamei 2011	- 2-methacryloxyethyl phosphorylcholine - n-butyl methacrylate - Paclitaxel Diameter: 50nm	MKN45P cells 3x10 ⁶	Female specific-pathogen-free conditioned BALB/c nude mice - Paclitaxel NP administrated IV - Paclitaxel NP administrated IP 5 µg/g - Paclitaxel solution	Paclitaxel penetration in tumor nodules was deeper with paclitaxel NP administrated IP compared to other groups. NP administrated IP were also found in hypovascular areas
Cirstoiu-Hapca 2010	- Poly(DL-lactic acid) -Taxol® - Herceptin	SKOV-3 5x10 ⁶	Females BALB/cOlaHsd mice - Taxol-NP-Herceptin -Taxol® solution	Tissue concentrations were higher when Taxol® was administered as nanoparticles due to the presence of antibodies at the particle surface.

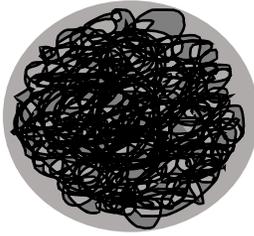
	<p>Diameter: 237±43 nm. About 250 molecules of mAbs were bound per nanoparticle</p> <p>Drug loading : 7.8±0.8% (w/w)</p>	<p>An initial dose of 20 mg/kg administered 10 mg/kg IV via the tail vein and 10 mg/kg IP, followed by five alternative IP and IV injections of 10 mg/kg every 3 days</p>	<p>Survival rate was improved with Taxol-NP-Herceptin.</p> <p>50 days after the end of the treatment, the tumors started to grow again in all treated mice.</p>
<p>Kohane 2006</p>	<p>- Poly-(lactic-co-glycolic) acid (PLGA)</p> <p>Diameter : 265nm</p>	<p>Male SV129 mice</p> <p>- carrier fluid containing MP</p>	<p>NP caused fewer adhesions, because they were cleared rapidly from the peritoneum and subsequently trafficked to the filtering organs (spleen and liver). This may also suggest that they may not be suitable for sustained drug release</p>

Table 2: Nanoparticle data summarized.

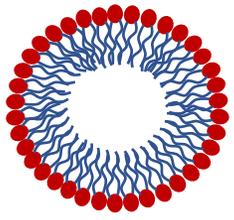
Drug delivery system	Advantages(s)	Inconvenient(s)
Microparticles	Prolonged residence time in peritoneal cavity depending on the particle size	Risk of adhesion Risk of inflammation
Nanoparticles	Small size allows tumor penetration enhancement	Spleen accumulation
Liposomes	Absence of toxicity and antigenicity Prolonged residence time in peritoneal cavity depending on the liposome size	
Micelles	Small size allows tumor penetration enhancement	Systemic passage Rapid elimination
Implants	Long term sustained release	Risk of fibrosis Risk of inflammation
Gel	Residence time prolonged in peritoneal cavity Homogenous repartition of drugs	Storage conditions
Gel + other DDS	Residence time prolonged in peritoneal cavity Drug realase prolonged Dual compartimentation	Storage conditions

Drug delivery system used to treat peritoneal carcinomatosis

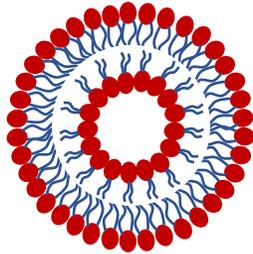
Particulate drug delivery systems



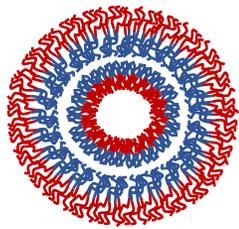
Micro/Nanoparticles



Micelles

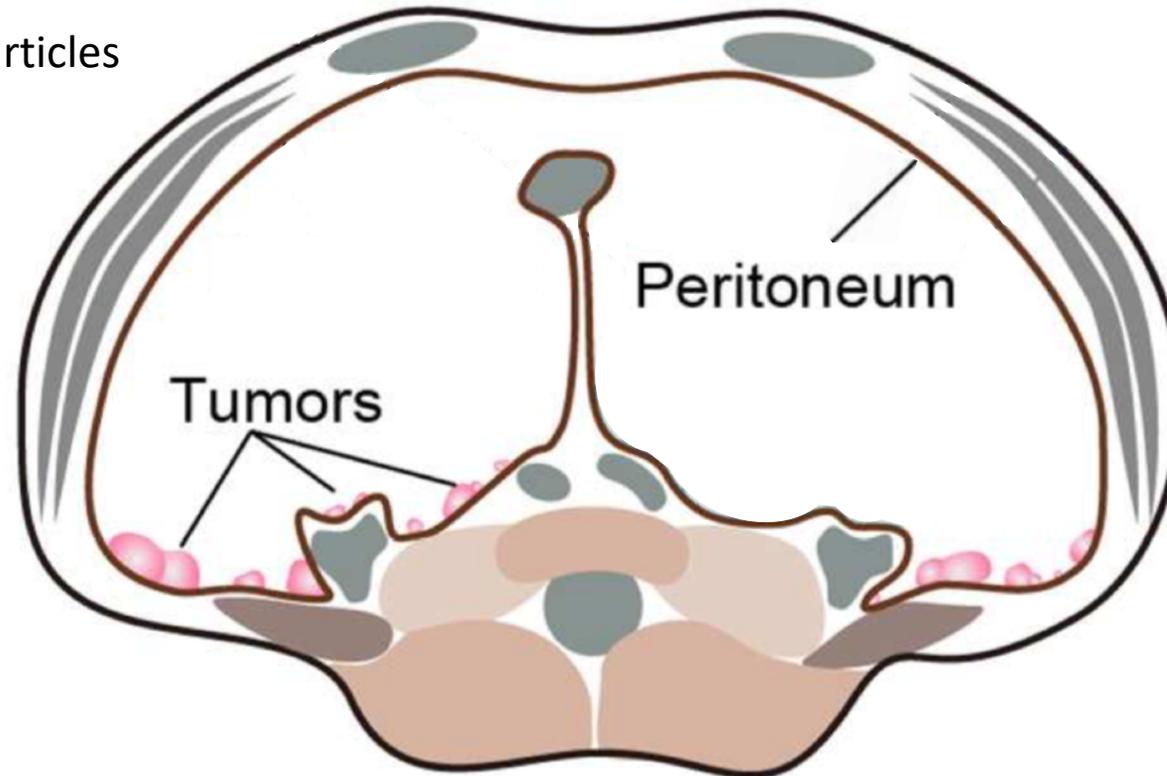
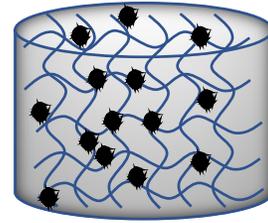


Liposomes

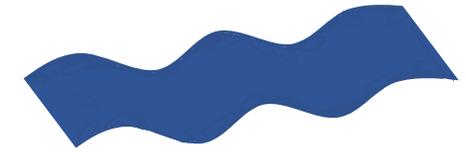


Polymersomes

Gels loaded with particles



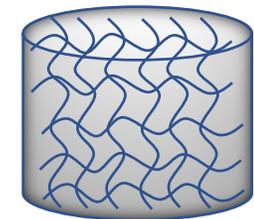
Non particulate drug delivery systems



Films



Implants



Gels