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1 **Iron oxide nanoparticles for therapeutic applications**

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3

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12

13 *Keywords:* Iron oxide nanoparticle, medical application, cancer, magnetic hyperthermia, therapy,  
14 nanotechnology, oncology, nanomedicine.

15

16 *Teaser:* Owing to their reassuring toxicity profiles and multiple mechanisms of action, iron oxide  
17 nanoparticles have been considered for a wide range of medical applications, including treatment of  
18 iron-deficiency anemia, cancer, Parkinson's, Alzheimer's, antibacterial and antifungal diseases.

19

20

21

22 In nanomedicine, iron oxide nanoparticles are at an advanced stage, being commercialized for cancer  
23 treatment and iron-deficiency anemia treatment. Their therapeutic efficacy comes from their ability to  
24 target a tissue, activate a drug, locally produce reactive oxygen species or a temperature increase  
25 following (or not) the application of an external source of energy, modify genes or activate various  
26 biological materials, or replace diseased cells by stem cells. Owing to these various mechanisms of  
27 action, they can potentially be used for treating a whole range of different diseases, making them more  
28 appealing than conventional drugs that target a more limited number of indications.

29

30

## 31 **Introduction**

32 Nanomaterials have been developed for medical applications owing to their appealing properties. First,  
33 their size is of the same order of magnitude as that of various biological materials such as enzymes,  
34 proteins and lipids, hence promoting interactions with them, and they are larger than most individual  
35 molecules used as standard drugs, resulting in better tissue interaction and larger accumulation in  
36 targeted organs for nanomaterials than for standard drugs. Second, nanomaterials have a large exposed  
37 surface area, which enables them to adjust their properties by changing their surface charge,  
38 composition or chemistry, or by binding to their surface molecules of interest such as specific ligands or  
39 chemotherapeutic molecules.

40 These properties, which are stimulating from the point of view of research, make it hard to set up a well-  
41 established regulatory framework, hence delaying the use of nanomedicine for human treatments. In  
42 addition, because each group working on a different nanomaterial tries to highlight the advantages of its  
43 system compared with others, it is difficult to identify a nanosystem that is better than others. However,  
44 iron oxide nanoparticles (IONPs) have paved the way among the most widely studied nanomaterials,  
45 owing to their biocompatibility and multiple ways in which they can trigger therapeutic activity. In this  
46 review, after a brief presentation of IONP manufacturing methods and physicochemical properties, the  
47 different mechanisms of action as well as treatments for specific diseases in which IONPs are involved  
48 are described.

49

## 50 **Fabrication and physicochemical properties of IONPs**

51 Methods to synthesize IONPs include: (i) co-precipitation between  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  in basic conditions [1];  
52 (ii) thermal decomposition of organo-iron in high boiling point organic solvents in the presence of  
53 surfactants [2]; (iii) nanoparticle formation inside micelles [3]; (iv) sol-gel methods [4]; (v)  
54 hydrothermal synthesis [5]; and (vi) cathodic electrochemical deposition in which anode oxidation leads  
55 to the formation of metal ions that are further reduced to metals by the cathode in the presence of a  
56 stabilizing material [6]. These synthesis methods enable obtaining IONPs with various sizes ~1–120

57 nm, size distributions, compositions [essentially consisting of  $\text{Fe}_3\text{O}_4$  (magnetite) and  $\gamma\text{-Fe}_2\text{O}_3$   
58 (maghemite)], crystallinity (amorphous or crystalline structure), magnetic properties (essentially  
59 superparamagnetic for IONPs <10–20 nm and ferrimagnetic for IONPs >10–20 nm) and geometries  
60 (spherical, round, square, cubic, cubo-octahedric, needle, cylindrical, cigar, bullet type). To prevent  
61 IONPs from aggregating, which can lead to embolism, these nanoparticles can be coated by various  
62 materials including polymers and fatty or amino acids. Furthermore, the coating material can influence  
63 nanomaterial biodistribution by controlling opsonization mechanisms; the capacity of specific cells such  
64 as macrophages to capture IONPs, for example polyethylene glycol (PEG), leads to a longer blood  
65 circulation time than citric acid [7–10].

66

### 67 **IONP targeting methods**

68 For IONPs to be efficient, they need to reach the organ of interest. As illustrated in Figure 1, this can be  
69 achieved through three different types of targeting mechanisms:

- 70 • Passive targeting also called enhanced permeability and retention (EPR) effect in which IONPs  
71 target tumors by passively diffusing through the holes of abnormal vessels resulting from  
72 angiogenesis that irrigate the tumor.
- 73 • Active targeting in the absence of magnetic field application, which relies on the use of IONPs  
74 conjugated with a targeting ligand (TL), which specifically targets a specific receptor that is  
75 overexpressed at the surface of cancer cells (T). Examples of pairs (TL:T) are: (i)  
76 antibody:antigene, such as antibody-Her-Neu:receptor-Her-2-neu [11]; (ii) aptamer:tumor-cell-  
77 receptor, such as anti-Muc-1:Muc-1 [12]; (iii) protein:tumor-cell-receptor, such as RGD: $\alpha v\beta_3$   
78 [13]; (iv) peptide:various-tumor-parts, such as F3::tumor-vasculature [14]; (v) enzyme:cell-  
79 receptor, such as uPA:uPAR [15]; (vi) vitamin:tumor-cell-receptor, such as folic-acid:folate-  
80 receptor [16]; (vii) chemical-compound:tumor-cell-receptor, such as methotrexate:folate-

81 receptor [17]; and (viii) hormone:tumor-cell-receptor, such as luteinizing hormone releasing  
82 hormone (LHRH):LHRH-receptor [18].

- 83 • Magnetic drug targeting, in which a strong external magnetic field gradient is applied to drive  
84 IONPs into the area of interest.

85 Taking the literature as a whole, it appears that the targeting efficacy is relatively similar for different  
86 targeting, yielding a percentage of injected IONPs in the tumor of  $5.10^{-4}\%$  to 3%, 0.1% to 7% and  $5.10^{-3}\%$   
87 to 2.6% for passive, active and magnetic targeting, respectively [19]. Next, the different mechanisms  
88 through which IONPs can generate a therapeutic activity, as summarized in Figures 1 and 2, are  
89 reviewed.

#### 91 **IONP drug delivery without a mechanism of drug release**

92 Although, in several cases, drug delivery using IONPs was described without mentioning a specific  
93 mechanism of drug release, this does not mean that such a mechanism did not occur. Disregarding such  
94 a mechanism, the conjugation of various chemotherapeutics to IONPs can be used to deliver these drugs  
95 to tumors, yielding the following advantages compared with the injection of free drugs: (i) the possibility  
96 to localize IONPs and therefore also possibly the drug conjugated to IONP, using MRI for example; (ii)  
97 the increase in drug accumulation in the tumor, for example IONPs containing doxorubicin (DOX) led  
98 to a higher concentration of DOX in tumor cells compared with free DOX treatment in an ovarian  
99 cancer model [19]; (iii) the association of drugs to IONPs can improve antitumor activity, for example  
100 IONPs conjugated with vinblastine led to enhanced MCF-7 breast cancer cell inhibition compared with  
101 vinblastine alone [20]; (iv) the combination of IONPs with a chemotherapeutic drug such as  
102 gemcitabine or mitoxantrone and a targeting agent such as anti-CD44 or prostate-specific membrane  
103 antigen (PSMA) antibodies can enhance drug targeting and antitumor efficacy on tumor cells compared  
104 with free drugs [21–24]; and (v) IONPs can be combined with a specific entity to prevent DNA pro-  
105 tumor activity, for example DNA was captured by cytarabine attached to IONPs [25].

106

## 107 **Drug delivery and activation with a mechanism of drug release**

108 Delivery and activation of drugs associated to IONPs can occur via various mechanisms:

- 109 • pH variation, which has been described for drugs such as 5-FU, curcumin, DOX and tamoxifen  
110 that either involve magnetic-polymer, PEG or IONPs inserted within the large pores of  
111 mesoporous hydroxyapatite-coated IONPs, or bind to monoclonal antibody (mAb)-conjugated  
112 magnetic nanocarriers, where release is more pronounced at an acidic cellular pH of 5.8 than at  
113 the blood pH of 7.4, leading to an increase of the percentage of drug release from 10–55% at pH  
114 7.4 to 70–85% at pH 5.8 [26,27].
- 115 • Temperature variation, which has been highlighted in systems containing: (i) curcumin  
116 incorporated in a nanogel containing a thermosensitive polymer (PNIPAM) and IONPs,  
117 releasing 35% and 70% of curcumin at 37°C and 41°C [28]; (ii) DOX bound to IONPs through  
118 an Azo linker, which is destroyed above ~43°C, when exposed to near infrared (NIR)  
119 irradiation, leading to DOX release and inhibition of tumor growth inhibition [29]; (iii)  
120 gemcitabine encapsulated together with IONPs inside a phospholipid bilayer to form a magneto-  
121 liposome, leading to an increase of drug release from 17% at 37°C without alternating magnetic  
122 field (AMF) application to 70% following AMF application [30].
- 123 • Magnetic field through either an indirect mechanism (i.e., the magnetic field causes nanoparticle  
124 cellular internalization of a drug bound to IONPs, such as BCNU-loaded nanocomplex in HG  
125 cells, resulting in drug release in the acidic cellular environment) [31] or a direct mechanism  
126 {i.e., the magnetic field itself causes drug release, as observed for IONP nanocapsules  
127 containing drugs surrounded by thermo-labile polymer (PEO-PPO-PEO) [32], IONP surrounded  
128 by a hydrophobic poly(vinyl alcohol) coating containing hydrophilic DOX, fluid MAG-CMX  
129 conjugated to DOX or magnetic polyerosomes loaded with DOX [33]}.
- 130 • Water or buffer surrounding IONPs that can trigger drug release as observed for 5-FU or  
131 curcumin progressively detaching from IONPs in water or different buffer solution [34],

possibly leading to enhanced cytotoxicity against tumor cells as highlighted for F@BSA@CUR in MCF-7 cells [34].

- IONP shape can have an impact on drug release mechanism, as observed for 5-FU bound to IONPs of various shapes [35].
- Drug circulation time in the organism can influence drug release, as observed for polyplex-coated magnetite (Nano-co-Plex) loaded with BCNU, which shows a time-dependent release efficacy with maximum release of 75% of the loaded BCNU [36].
- Breaking of the bond between the drug and the IONPs, using either acidic conditions or specific biological materials (proteinase), as described for: (i) L-lysine surface-coated IONPs conjugated with methotrexate (MTX), where the peptide bond is cleaved in the presence of proteinase K at low pH [37]; (ii) for IONPs bound to polyethylene glycolated methotrexate (MTX-PEG) and NIR fluorescent cyanin dye (Cy5.5) that could be hydrolyzed at intracellular pH, preventing drug release in systemic circulation while allowing it inside endosomes or lysosomes [38]; (iii) for IONPs linked to drugs through bounds that are cleaved by tumor enzyme-cleavable peptides such as lysosomal proteases [39].

These mechanisms of selective drug release can prevent side effects as highlighted when the highly cytotoxic drug azademethylcolchicine (ICT) was conjugated to the dextran layer of the IONP ferumoxitol using a peptide linker, which was cleavable by matrix metalloproteinase-14 (MMP-14), leading to significant tumor cell apoptosis while sparing healthy cells [40].

### **Intracellular drug delivery with IONPs**

If a drug is not delivered intracellularly it can lose its activity, for example by diffusing in the bloodstream or by being eliminated. Drugs associated with IONPs can more easily internalize in cells than free drugs because the size of the drug–IONP complex is significantly larger than that of free drugs, a ligand can be bound to the IONP surface that specifically binds a cell receptor. As an example,



157 direct intracellular drug delivery of DOX by IONPs was shown to be much more efficient than that of  
158 free DOX for targeting and concentrating DOX within a Hep-G2/MDR tumor site [41].

159

### 160 **IONP therapy working through the production of ROS**

161 IONPs could trigger some activity by releasing radical oxygen species (ROS) as demonstrated either  
162 when IONPs are dissolved into  $\text{Fe}^{2+}$  and/or  $\text{Fe}^{3+}$ , for example following IONP cellular internalization  
163 and degradation by lysosomes [42], or when a substance bound to IONPs produces ROS, as shown for  
164 cisplatin attached to IONPs, which activated nicotinamide adenine dinucleotide phosphate oxidase  
165 (NOX), transforming di-oxygen ( $\text{O}_2$ ) to superoxide radical ( $\text{O}_2 \bullet^-$ ) and  $\text{H}_2\text{O}_2$ , resulting in the apparition  
166 of toxic hydroxyl radicals ( $\bullet\text{OH}$ ) through the Fenton's reaction between  $\text{H}_2\text{O}_2$  and  $\text{Fe}^{2+}$  [43].  
167 Furthermore, ROS, such as  $\bullet\text{OH}$ , have been shown to induce oxidative damage to lipids, proteins and  
168 DNA in the tumor site while minimizing systemic toxicity [43].

169 ROS can also be produced by exposing a photosensitizing agent associated with IONPs to a laser  
170 through a technique called photodynamic therapy (PDT). In this case, IONPs are used as a platform or  
171 support for binding a large number of photosensitizing agents such as hypericin. The efficacy of such an  
172 approach was demonstrated on a complex of red blood cells, DOX, IONPs and chlorine e6 that  
173 significantly suppressed tumor growth using PDT [44].

174

### 175 **IONP therapy based on local temperature increase (magnetic hyperthermia and photothermal 176 therapy)**

177 Localized heat can be produced by exposing IONPs to the following:

- 178 • An AMF using a technique called magnetic hyperthermia (MHT), where the AMF should have  
179 frequency and strength  $>20\text{--}100$  kHz and 1-10 mT, respectively, and IONP should be  
180 sufficiently concentrated (i.e., typically above 1 mg of IONP per  $\text{cm}^3$  or ml of surrounding  
181 medium) [41], resulting in specific absorption rate (SAR) of typically 1 to 1000 W/gFe,  
182 depending on IONP properties (size, anisotropy stability of magnetic moment) and AMF

183 parameters, leading to a series of different therapeutic activities (i.e., specific tumor cell  
184 destruction without destruction of healthy cells) [41,42]; (ii) significant or full tumor destruction  
185 on mice bearing different tumor types (e.g., subcutaneous or intracranial) [45–50]; (iii)  
186 activation of a drug such as DOX [51]; (iv) an improvement of GBM patient survival by ~7  
187 months [44,52]; (v) significant lesion reduction by implanting a composition of IONPs and  
188 calcium phosphate cement in bone tumors [53]. A typical protocol used for MHT treatment is  
189 illustrated in Figure 3.

- 190 • A laser using photothermal therapy (PTT), which produces a localized surface plasmon wave  
191 using laser wavelengths in the NIR within 650–900 nm to avoid harmful light absorption by  
192 healthy tissues, and laser power is maintained below the safe limit of tissue irradiation of 0.3–1.0  
193 W/cm<sup>2</sup>, resulting in the destruction of tumor cells (e.g., MCF-7 and MDA-MB-231) or full or  
194 partial tumor disappearance in mouse without apparent side effects, where therapeutic activity  
195 was observed in the absence and in the presence of an absorbing material such as PPy [28].

196 These nanoparticle-based heating techniques present the advantage of moderately heating the tumor  
197 during treatments at typically 41–55°C, which limits side effects compared with 80–90°C reached in  
198 cancer thermotherapies that do not use nanoparticles such as HIFU and radiofrequency.

199 Mechanisms to explain antitumor efficacy with MHT and PTT rely on: (i) structural and functional  
200 cancer cell damage, specifically at the level of protein, membrane and cytoskeleton, which can lead to  
201 apoptosis [54]; (ii) ‘fragilization’ of cancer cells which increases the sensitivity of these cells to other  
202 treatments such as chemotherapy or radiotherapy [55]; (iii) expression of heat shock proteins at  
203 temperatures of typically 41–46°C that can attack the tumor [56], although the opposite behavior  
204 (protection of the tumor) has also been reported for these proteins [57]; (iv) protein denaturation or  
205 unfolding that can occur at high temperature; (v) pH changes, perfusion and oxygenation of the tumor  
206 microenvironment that can lead to tumor necrosis [58]; and (vi) apoptosis or necrosis depending on  
207 treatment parameters (temperature, duration of heating, etc.) [45].

## 209 **Triggering gene therapy with IONPs**

210 IONPs could potentially improve gene therapy efficacy by carrying specific nucleic acids that regulate  
211 altered gene expression resulting from carcinogenesis, essentially in the form of siRNA or plasmid  
212 DNA. An IONP–gene complex could have a larger circulation time than that of a free gene, avoid  
213 potential damages by nucleases and hence enable nucleic acids delivery to the organ of interest such as a  
214 tumor [59]. Such therapy could act against a tumor in the following ways:

- 215 • Directly, for example when IONPs conjugated with siRNA (siPLK1) act against Pololike kinase-  
216 1 (cell-cycle-specific serine/threonine kinase) and two peptides (MPAP and MUC1) were  
217 injected in tumor-bearing mice, the result is the accumulation of IONPs in the tumor, efficient  
218 PLK1 silencing and tumor suppression through increased apoptosis [60].
- 219 • Indirectly, for example when IONPs carrying the phosphatase and tensin homolog (PTEN) gene  
220 increased the sensitivity of A549/CDDP lung cells to cisplatin treatment indicating that PTEN  
221 can effectively be used against cisplatin-resistant lung cancer cells [61].

222 Furthermore, to improve the efficacy of gene therapy, the IONP–gene complex can be attracted near the  
223 tumor by a magnet, hence increasing gene transfer into cells [62], via a technique called magnetofection.  
224 To date, clinical trials testing gene therapy have been unsuccessful owing to the existence of a multitude  
225 of different genes responsible for cancer, depending on cancer type, cancer progression and type of  
226 cancer patient, which can hardly all be targeted with only one gene therapeutic agent [63]. To further  
227 improve the efficacy of gene therapy, it might be suggested to use IONPs to: (i) carry out a pre-  
228 screening of pro-tumor genes for each patient taken individually and adapt gene therapy depending on  
229 the detected genes; (ii) use a combination of different genes instead of only one gene to increase the  
230 probability of targeting pro-tumor genes; or (iii) combine gene therapy with another modality of  
231 treatment.

232

## 233 **Stem cell therapy using IONPs**

234 IONPs can be used in stem cell therapy by being incorporated inside these cells, enabling them to  
235 localize, for example using MRI, and activating them with the help of magnetic actuation [64]. By using  
236 IONPs during the transplantation of oligo-dendrocyte precursor cells (OPCs), it might be possible to  
237 help in regenerating the central nervous system by increasing myelin production and hence restore the  
238 protective sheath around nerve fibers [65].

239

## 240 **Immunotherapy**

241 IONPs can act on the immune system in the following ways:

- 242 • They modulate macrophage polarization (i.e., inducing a shift from M2-type macrophages with  
243 anti-inflammatory and pro-tumor activity to M1-type macrophages with anti-tumor and  
244 proinflammatory activity), as was shown for example for THP-1 monocytes that shifted from a  
245 M2-like phenotype before IONP exposure toward a M1-like phenotype after IONP exposure  
246 [66].
- 247 • They increase the efficacy of immune-suppressive drugs used during organ transplantation, as  
248 was shown when mycophenolic acid (MPA) combined with IONPs and effectively inhibited the  
249 secretion of the cytokines interleukin (IL)-2 and tumor necrosis factor (TNF), with a  
250 concentration of MPA that is lower than that necessary to reach a similar effect in the absence of  
251 IONPs [67], hence reducing side effects observed at high MPA concentrations.

252

## 253 **Protein and enzyme activation or removal with IONPs**

254 It has been shown that IONPs can act like enzymes by mimicking the activity of peroxidase [60] and  
255 efficiently immobilize proteins at their surface owing to their large surface-area:volume ratio, and then  
256 separate or isolate proteins by applying an external magnetic field [68].

257

## 258 **Different types of diseases treated with IONPs**

259 A summary of the different types of diseases that can be treated with IONPs and the mechanisms of  
260 action that are involved in the treatments is provided in Figure 4 and Table 1. Cancer can be treated  
261 through the generation of ROS or localized heat by IONPs or via a chemotherapeutic drug associated  
262 with IONPs, where the IONP–drug complex can lead to the following:

- 263 • An enhanced efficacy of chemotherapeutic drug, for example: (i) IONPs associated with  
264 paclitaxel (IONP–PAX) are more cytotoxic than free PAX in destroying prostate tumor cells, as  
265 demonstrated *in vitro* on PC3 and CWR22R human prostate cancer cells [69] and *in vivo* on C4-  
266 2-cell-derived xenograft tumors in athymic nude mice [69]; and (ii) IONPs associated with DOX  
267 are more cytotoxic toward 4T1 cells than free DOX [70].
- 268 • A reduction of toxicity of certain anticancer drugs such as docetaxel, mitoxantrone, cisplatin and  
269 carboplatin by increasing the efficacy of tumor drug delivery and by simultaneously reducing the  
270 dose necessary to reach therapeutic efficacy, as shown for IONPs conjugated to docetaxel, which  
271 led to enhanced cellular uptake ability and antiproliferative activity in PC3 prostate cancer cells,  
272 and for toxic mitoxantrone where tumor uptake was increased when it was conjugated with  
273 IONPs [69], overcoming the cytotoxicity induced by certain chemotherapeutics (cisplatin,  
274 carboplatin).
- 275 • An increase in drug-targeting efficacy through the use of: (i) stimuli-responsive drug release  
276 from IONPs, for example with a higher drug release at pH 5.8 (mimicking the tumor  
277 microenvironment) than at pH 7.4 (normal physiological condition); (ii) targeting agents that are  
278 able to target specific receptors of cancer cells as summarized above.
- 279 • Chemosensitization of tumor cells to chemotherapeutic drug, as was shown through the  
280 cytotoxicity enhancement of cisplatin toward cisplatin-resistant A549 tumor cells using IONPs  
281 loaded with cisplatin [71].

282 In addition to the mechanisms described above, it has been reported that IONPs can modify the tumor  
283 microenvironment by blocking an artery that irrigates the tumor with blood [72]. Alzheimer’s disease  
284 (AD) could be treated by IONPs functionalized by a targeting agent that can cross the blood–brain

285 barrier (BBB) and reach small peptides called amyloid- $\beta$  (A $\beta$ ) and then either detect A $\beta$  using MRI or  
286 affect the A $\beta$  fibrillation process, responsible for AD, with an efficacy that seems to depend on IONP  
287 size, surface area, charge, concentration and level of opsonization [73]. Parkinson's disease (PD) could  
288 be treated by IONPs using the following:

- 289 • Gene therapy, by conjugating IONPs with short hairpin RNA (shRNA), promoting neuronal  
290 uptake via nerve growth factor (NGF) receptor-mediated endocytosis or neuron apoptosis caused  
291 by a lower  $\alpha$ -syn expression *in vitro* and *in vivo*, leading to effective repair in a PD model [74].
- 292 • Magnetic field therapy, by applying a magnetic field on rats at the site of PD lesion 24 h after  
293 IONP administration, 2 h/day for 1 week, leading to an improved behavior, condition,  
294 mitochondrial function and attenuation of lesion volume in all treated rats, indicating the  
295 neuroprotective effect of this therapeutic approach [75].

296 Neuro-AIDS, which refers to a reservoir of AIDS viruses in the brain, could potentially be treated by  
297 attaching conventional treatments (tenofovir and vorinostat) to IONPs to enable these drugs to cross the  
298 BBB and to efficiently eradicate AIDS viruses in the brain, as demonstrated by IONP antiviral activity  
299 *in vitro* over a period of 5 days after HIV infection in primary human astrocytes [76]. Iron-deficiency  
300 anemia, which cannot be efficiently cured with oral iron treatment owing to drug gastrointestinal  
301 digestion, could be treated with intravenous injection of IONPs, improving iron biodisponibility; and  
302 this has been commercialized in formulations such as Dexferrum<sup>®</sup>, Feraheme<sup>®</sup>, Ferrisat<sup>®</sup>, Ferrlecit<sup>®</sup>,  
303 Monofer<sup>®</sup> and Venofer<sup>®</sup> [19].

304 Fungi or bacterial contamination can be eradicated by inhibiting the growth of fungi such as  
305 *Trichophyton verrecosum*, *Trichophyton mentagrophytes*, *Dermatophilus sp.*, *Trichothecium roseum*,  
306 *Cladosporium herbarum*, *Penicillium chrysogenum*, *Alternaria alternata* and *Aspergillus niger* [77] or  
307 bacteria such as *Escherichia coli*, *Bacillus subtilis*, *Candida albicans*, *Aspergillus niger* and *Fusarium*  
308 *solani* [78]. Growth inhibition can be the result of leakage of the cell contents leading to cell death,  
309 inhibition of spore germination, membrane destruction, production of ROS with lipid peroxidation,  
310 DNA damage, release of metal ions and/or the presence of antibacterial or antifungal substances

311 associated with IONPs such as vanilla essential oil, antibiotics and chlorhexidine (CHX). Furthermore,  
312 IONPs can penetrate inside biofilms and hence yield efficient biofilm destruction, a property that seems  
313 to depend upon IONP physicochemical characteristics, such as IONP surface charge, hydrophobicity  
314 and high surface-area:volume ratio [79]. Blood contamination can be treated by attaching IONP  
315 molecules that specifically bind to contaminant material, such as pathogens or toxic compounds, as  
316 shown for IONPs colliding with *Staphylococcus aureus*, internalizing inside these bacteria and then  
317 being removed under magnetic field application [80]; or for IONPs surrounded by a specific coating that  
318 can bind radioactive material or heavy metal.

319

### 320 **Concluding remarks and future perspectives**

321 Despite their huge potential, IONPs are currently only commercialized for treatment of iron-deficient  
322 anemia (e.g., Venofer<sup>®</sup> commercialized by American Regent) and cancer treatment (e.g., Nanotherm<sup>®</sup>  
323 sold by Magforce). To foster IONP commercialization for other indications, new developments can be  
324 carried out such as: (i) IONP synthesis methods that do not contain toxic products and yield sufficient  
325 production of highly pure and stable IONPs; (ii) IONPs that can be activated on demand by applying an  
326 external source of energy, only when they are located in the organ to be treated, hence avoiding IONP  
327 side effects on healthy tissues; and (iii) an energy source that is affordable and can easily be used by  
328 doctors, especially within the hospital environment.

329

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338 directed the research presented in this article.

339

340 **Conflicts of interest**

341 Edouard Alphandéry has been working at the start-up Nanobacterie.



342 **Figure legends**

343 **Figure 1.** Schematic representation of iron oxide nanoparticle (IONP) therapeutic mechanisms of action  
344 through chemotherapeutic drug release and activation, heat and reactive oxygen species (ROS)  
345 production, under application (or not) of an external source of energy. Schematic illustration of the three  
346 targeting mechanisms (passive, active, magnetic targeting).

347 **Figure 2.** Iron oxide nanoparticle (IONP) mechanisms of action can be subdivided between: (i) IONP  
348 local temperature increase (PTT, MHT); (ii) gene therapy (intentionally or non-intentionally triggered);  
349 (iii) reactive oxygen species (ROS) production (PDT or due to IONP themselves); (iv) drug delivery  
350 caused by the release of drugs initially attached to IONPs; (v) IONP targeting of specific cells or  
351 biological entities through active, passive or magnetic targeting.

352 **Figure 3.** Example of iron oxide nanoparticle (IONP) treatment using magnetic hyperthermia by  
353 administering IONPs to a tumor and then heating IONPs under alternating magnetic field application.  
354 The mechanisms of action involve moderate local heating at typically 42–50°C followed by death of  
355 cancerous cells.

356 **Figure 4.** Iron oxide nanoparticle (IONP) therapeutic applications including treatment of neuro-AIDS,  
357 cancer, blood contamination, Alzheimer's disease and Parkinson's disease, where the treatments rely on  
358 antifungal, antibacterial, antitumoral, nanozyme or immunotherapy.

359

360 **References**

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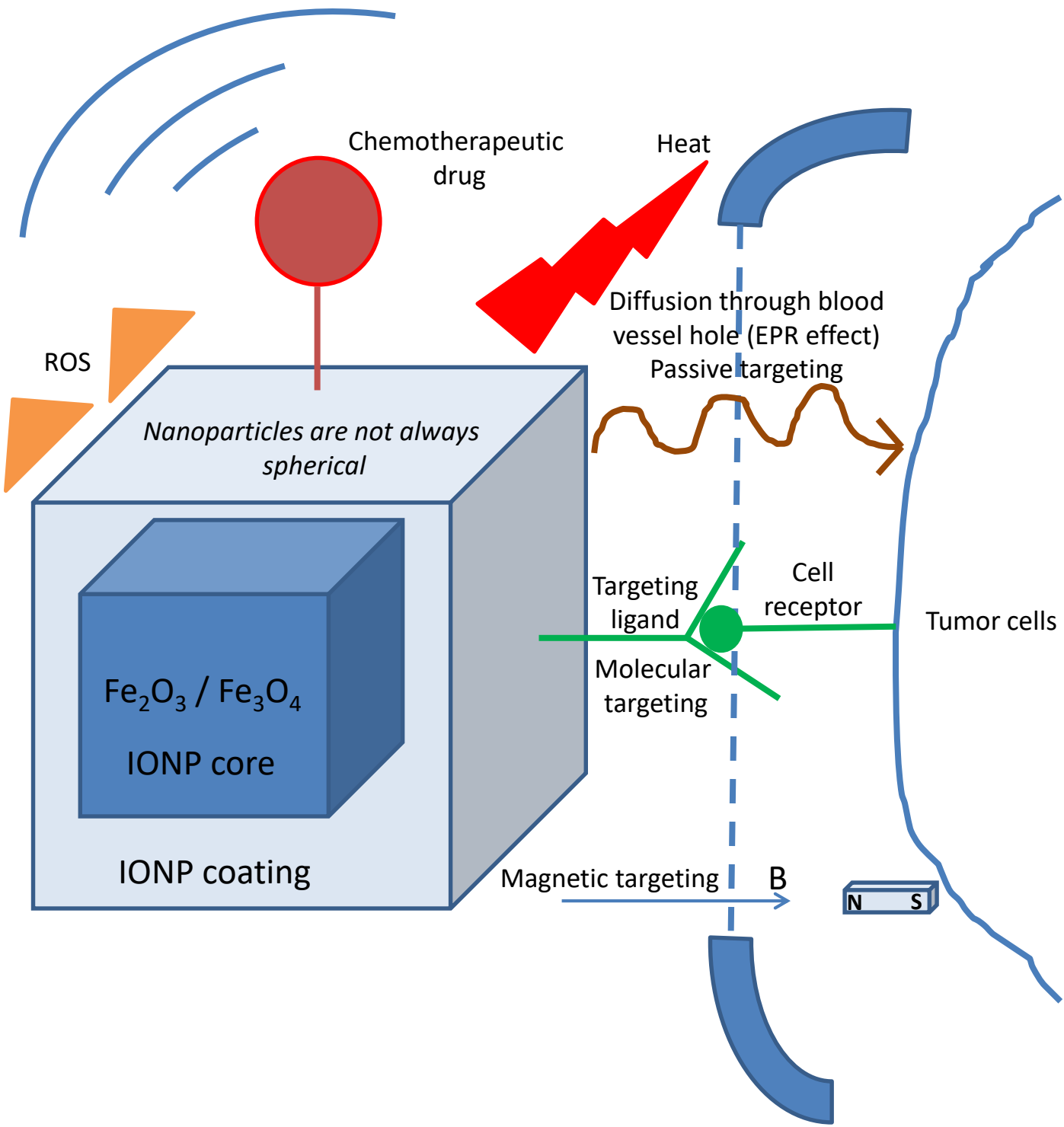
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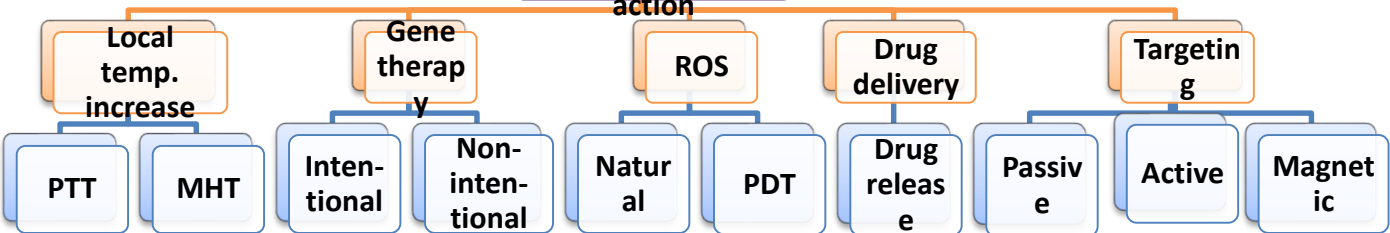
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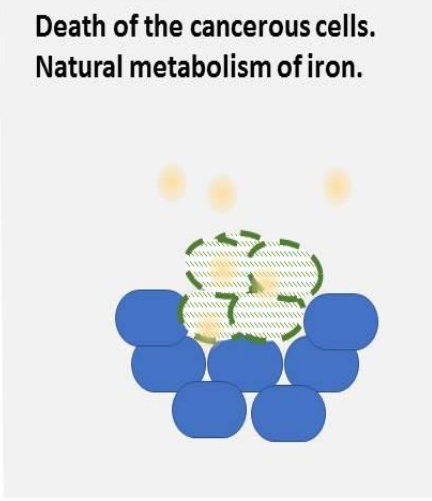
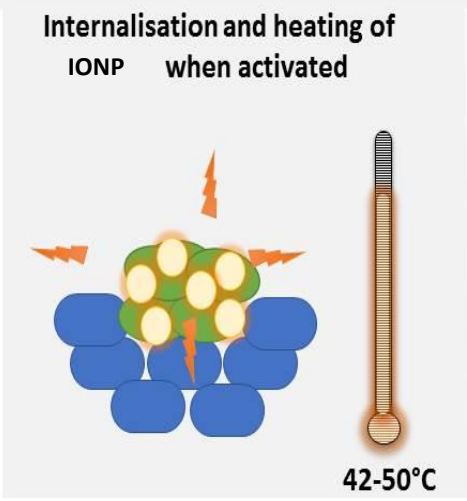
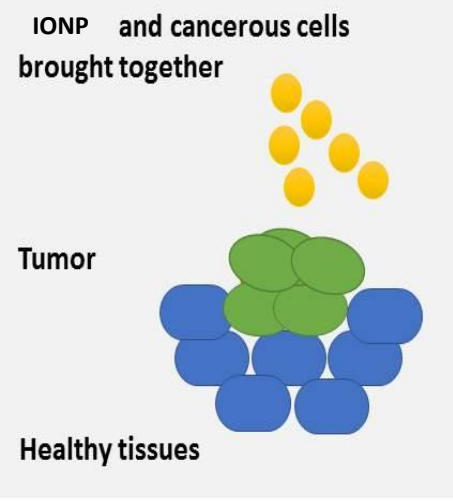
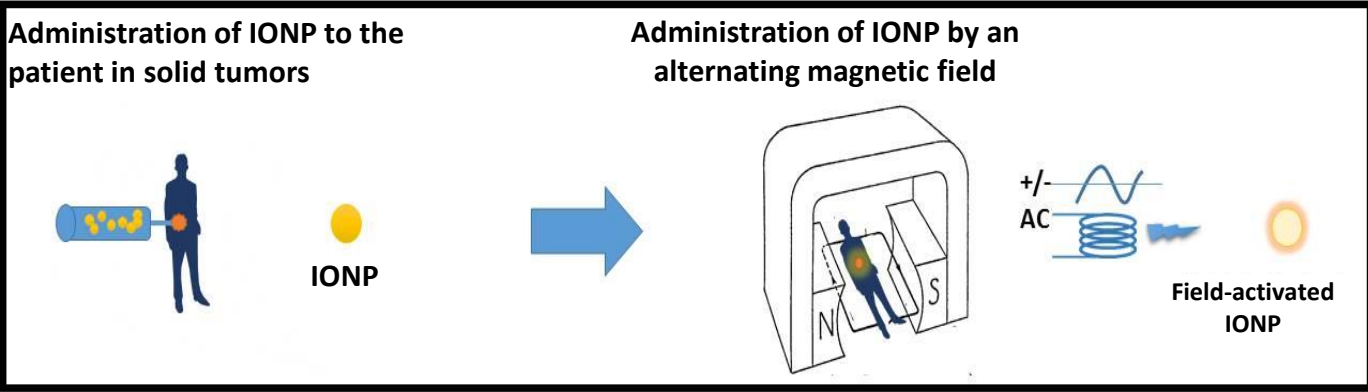


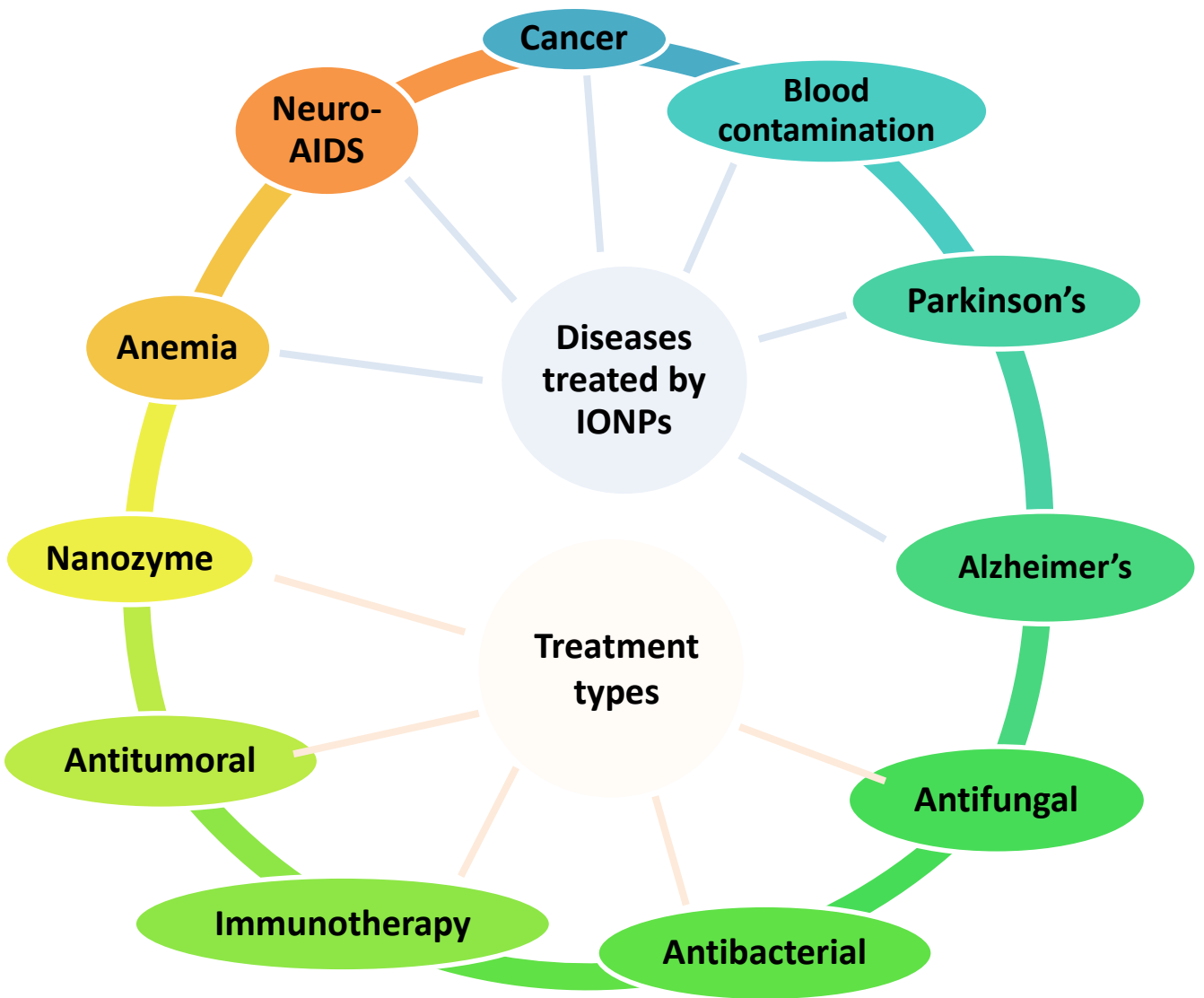
Excitation by an external source of energy  
Magnetic field, ultrasound, laser



**IONP  
mechanism of action**







Types of treated diseases	Mechanisms involved in treatment	Experimental conditions (Cellular/animal/human)
Cancer	Enhanced chemotherapy	IONP-PAX more efficient than free PAX: <ul style="list-style-type: none"> <li>○ <i>in vitro</i> on PC3/CWR22R cells [69]</li> <li>○ <i>in vivo</i> on C4-2 mouse tumors [69]</li> </ul>
	Reduction of toxicity of anticancer drugs	Tumor uptake of mitoxantrone increased with IONP by reducing therapeutically efficient dose of mitoxantrone shown <i>in vitro</i> and <i>in vivo</i> [69]
	Increase in drug-targeting efficacy	Stimuli drug release as a function of: <ul style="list-style-type: none"> <li>○ pH variation (<i>in vitro</i> [26])</li> <li>○ Temperature variation (<i>in vivo</i> [27])</li> <li>○ Magnetic field (<i>in vitro</i> [30])</li> <li>○ Water/buffer (<i>in vitro</i> [34])</li> </ul>
	ROS	IONPs produce ROS: <ul style="list-style-type: none"> <li>○ by themselves (Fenton reaction) (<i>in vitro</i> and <i>in vivo</i> [43])</li> <li>○ following laser excitation (PDT) (<i>in vivo</i> [44])</li> </ul>
	Localized heat	<ul style="list-style-type: none"> <li>○ MHT (human [52])</li> <li>○ PTT (<i>in vitro</i> [28])</li> </ul>
	Prevent tumor growth	Blocking the blood artery that irrigates the tumor and promotes tumor growth ( <i>in vivo</i> [72])
Alzheimer's	Acts on fibillation process	Therapy/diagnosis ( <i>in vitro</i> , <i>in vivo</i> [73])
Parkinson's	Gene therapy	Inhibition by IONP-RNAi ( <i>in vitro</i> , <i>in vivo</i> [74])
	Magnetic field therapy	Neuroprotective ability of IONPs under magnetic field exposure ( <i>in vivo</i> [75])
Neuro-AIDS	Enables AIDS drugs to cross blood–brain barrier	Proposed model for <i>in vitro/in vivo</i> /human configurations [76]
Iron-deficiency anemia	Enhances iron bioavailability	Commercially available to treat IAD [19]
Fungi/bacteria contamination	Destroys fungi/bacteria through ROS production/DNA damages	IONP activity demonstrated directly on fungi/bacteria [77–79]
Blood contamination	Removal of blood contaminants using IONP	Capture of blood bacteria by IONP demonstrated <i>in vitro</i> [80]

**Table 1. Types of diseases treated with IONPs; mechanisms involved in the treatment; experimental demonstration; associated references**

Abbreviations: PAX, paclitaxel; PDT, photodynamic therapy; MHT, magnetic hyperthermia; PTT, photothermal therapy; RNAi, RNA interference; IAD, iron anemia disease.