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1 ***From molecules to nanovectors: current state of the art and***
2 ***applications of photosensitizers in photodynamic therapy***

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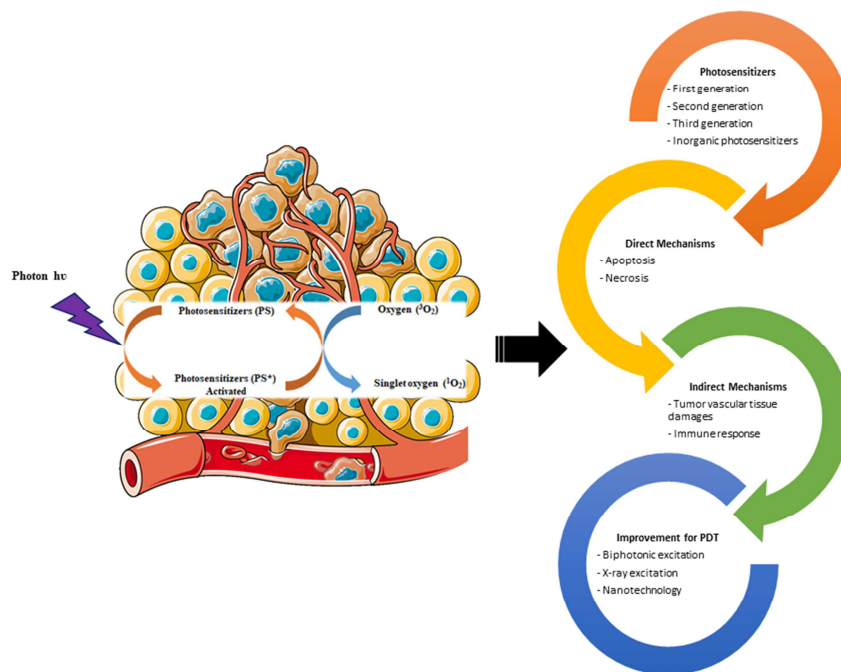
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11

12 **Graphical abstract**

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Abstract

Photodynamic therapy (PDT) is a concept based on a selective activation by light of drugs called photosensitizers (PS) leading to reactive oxygen species production responsible for cell destruction. Mechanisms of photodynamic reaction and cell photo-destruction following direct or indirect mechanisms will be presented as well as PS classification, from first generation molecules developed in the 1960s to third generation vectorized PS with improved affinity for tumor cells. Many clinical applications in dermatology, ophthalmology, urology, gastroenterology, gynecology, neurosurgery and pneumology reported encouraging results in human tumor management. However, this interesting technique needs improvements that are currently investigated in the field of PS excitation by the design of new PS intended for two-photon excitation or for X-ray excitation. The former excitation technique is allowing better light penetration and preservation of healthy tissues while the latter is combining PDT and radiotherapy so that external light sources are no longer needed to generate the photodynamic effect. Nanotechnology can also improve the PS to reach the tumor cells by grafting addressing molecule and by increasing its aqueous solubility and consequently its bioavailability by encapsulation in synthetic or biogenic nanovector systems, ensuring good drug protection and targeting. Co-internalization of PS with magnetic nanoparticles in multifunctional vectors or stealth nanoplateforms allows a theranostic anticancer approach. Finally, a new category of inorganic PS will be presented with promising results on cancer cell destruction.

Key-words: phototherapy dynamic, photosensitizer, cancer management, nanotechnology

40

41 **1. Introduction**

42 Phototherapy in its ancestral form has been used empirically in Chinese, Indian, Egyptian and
43 Greek civilizations. Simple photosensitizer-free phototherapy was performed mainly using the
44 beneficial effects of sunlight, for example in the prevention of local skin disease (Daniell and
45 Hill, 1991). Light is the source of many therapies among which we find photodynamic
46 therapy (PDT), which requires oxygen (Rkein and Ozog, 2014). PDT is a concept based on a
47 selective activation by light of drugs called photosensitizers (PS) (Gomes et al., 2018). These
48 drugs, non-toxic in the absence of excitation light have the ability to absorb light energy,
49 leading to an energy transition and transfer to the surrounding environment. This transfer
50 leads to reactive oxygen species (ROS) production, such as singlet oxygen, responsible for
51 cell destruction (Donohoe et al., 2019) and to luminescence properties (Celli et al., 2010). It is
52 accepted that the main agent responsible for the PDT effect is singlet oxygen (Fig. 1), even if
53 other agents are involved (Ochsner, 1997). Due to their very short shelf life and low diffusion
54 in biological media, the reactivity of ROS will be limited to their intracellular localization.
55 Using a localized light irradiation, the selectivity of PDT action allows to lyse cells while
56 preserving healthy cells. Light sources used can be lamps, fluorescent tubes, lasers, and more
57 recently electroluminescent diodes, possibly fitted with optic diffusers (Brancaleon and
58 Moseley, 2002). The fluorescence properties of PS are also an advantage allowing
59 visualization of patient tissues during PDT coupled with surgery. Oxidative stress induced by
60 PDT causes cell death by necrosis or apoptosis and can produce a variety of effects on
61 immune cells (Agostinis et al., 2011). The type of PS, its concentration, its subcellular
62 localization as well as the dose of light applied influence the effects of the photodynamic
63 treatment (Ratkay et al., 2000).

64 High dose PDT (i.e. high levels of PS and / or light) acts directly on tumor cells and indirectly
65 by destruction of the vascular endothelium following the release of tumor antigens and
66 activation of anti-tumor immune response (Agostinis et al., 2011). In contrast, low dose PDT
67 therapy may have immunomodulatory effects capable of treating different models of
68 autoimmune diseases or inflammatory disorders, while keeping cell viability intact (Doix et
69 al., 2019). The immunosuppressive effect of PDT was first noticed in 1986, with the
70 suppression of a contact hypersensitivity reaction in mice previously exposed to a hapten, one
71 of the two building blocks of an antigen (Elmets and Bowen, 1986).

72

73 **2. Principles of photodynamic therapy**

74 PDT is a technique whose biophysical principles were experimentally established 130 years
75 ago by Oscar Raab (Daniell and Hill, 1991; Raab, 1900). Preliminary work from Tappeiner
76 and Jesoniek showed that porphyrins were preferentially picked up by cancer cells, causing
77 red fluorescence when exposed to light with appropriate wavelength. Porphyrins were also
78 able to interact with light energy causing reactions leading to cell death (necrosis, apoptosis)
79 (Tappeiner and Jesoniek, 1903). Thus, PDT consists in sensitizing cancerous tissues to the
80 action of light by the prior injection of a photosensitizing molecule preferentially captured and
81 retained in cancerous tumors. Dougherty *et al.* made their first application in digestive
82 cancerology with hematoporphyrin derivative in 1978 (Dougherty et al., 1978). Following
83 intravenous injection, the inactive PS will reach and be captured preferentially by cancerous
84 tumors for various reasons partly linked to the histopathological texture of the cancerous
85 tissue (vascular and lymphatic richness, large interstitial sector and abundance of
86 macrophages), the hydro and liposolubility of the PS facilitating its penetration into neoplastic
87 cells (Chen et al., 2017). Then, the exposure of the tumor to colored laser-like light will cause
88 a photo activation defined by the change of state of the chromophoric molecules induced by

89 photons. By light absorption, the molecules acquire energy and pass from a S_0 ground state to
90 different excited states ($S_1, S_2 \dots$), the first state called “singlet” (S_1) is occupied directly or
91 after very rapid partial non-radiative deactivation of the higher states (Fig. 2). The excited
92 molecule has an excess of energy that will be released spontaneously either in the form of
93 heat or light. Two pathways of de-excitation by emission of light can be distinguished: i) a
94 quick de-excitation (order of nanoseconds) from the lowest singlet excited state S_1 leading to
95 a fluorescence (photo diagnosis) ii) a slow de-excitation (order of microseconds), from an
96 intermediate state known as “triplet” T_1 responsible for the phenomena of photosensitivity.
97 The PS can return to the fundamental state either by the emission of light or by transmitting
98 the excess of energy to molecular oxygen in its triplet ground state (3O_2) which is thus excited
99 affording singlet oxygen (1O_2). Then, the PS returns to its initial state and is ready for a new
100 collection of light energy. From the triplet state, in addition to singlet oxygen, free radicals
101 such as superoxide and hydroxyl are also formed (Chen et al., 2014). Although the entire
102 mechanism is not fully known, it seems that singlet oxygen and, to a lesser extent, free
103 radicals are the main cytotoxic agents. PDT-induced cytotoxicity is therefore mainly due to
104 oxidation phenomena leading to the degradation of amino acids, nucleic bases, lipids
105 composing cell membranes and mitochondria (Moan et al., 1998). PDT-induced cytotoxicity
106 is influenced by oxygen concentration in the tumor tissue, anoxic areas may exist within a
107 tumor explaining the unequal and partial efficacy of the treatment requiring additional
108 exposure (Weston and Patterson, 2014).

109

110 **2.1. Mechanisms of photodynamic reaction**

111 Photo-oxidation is the basic process of the photodynamic effects which are actually made up
112 of many chemical and biological reactions. In 1976, Weishaupt *et al.* associated the photo

113 inactivation of tumor cells to the singlet oxygen action as cytotoxic agent (Weishaupt et al.,
114 1976). Photo-oxidation can be divided into two stages which are presented below.

115

116 **2.1.1. Passage of the photosensitizer from the S_0 fundamental state to the T_1** 117 **excited triplet state following light absorption**

118 The photoreactive molecule is initially in the S_0 fundamental state. Following the absorption
119 of one photon, it will first find itself at a higher S_1 singlet type energy level. From this level, it
120 can return to the ground state following different pathways. The de-excitation can be either
121 non-radiative in the form of heat or radiative in the form of light which is called
122 photoluminescence. On the one hand, when the decay is done preserving the multiplicity of
123 spin (S_1 to S_0 transition) the emission of light is called fluorescence. This emission is fast in
124 the order of nanoseconds. On the other hand, an intersystem conversion between the singlet
125 state S_1 and the triplet state T_1 can be possible for which the multiplicity of spin is not
126 preserved. Although this non-radiative transition is normally prohibited, the PS on triplet T_1
127 state can then either return to the S_0 ground state emitting light through a slow
128 phosphorescence process (in the order of microseconds) or participate in the second stage of
129 the photo-oxidation reaction. It must be remembered that from S_1 singlet state level, the cross-
130 system conversion from S_1 to T_1 is not the only type of transition carried out as we can for
131 example observe fluorescence phenomena (Fig. 2). For the photodynamic effect to be
132 significant, it is necessary that the efficiency of the PS inter-system conversion from S_1 to T_1
133 is higher to the effectiveness of other S_1 deactivation processes. Thus, the quantum yield of
134 the intersystem crossover from S_1 to T_1 , noted Φ and defined as the ratio of the number of
135 reacting molecules according to the photo-oxidation process on the number of photons
136 absorbed by the system during the same time, will have to be high enough to allow the T_1

137 triplet state to be populated effectively and others deactivation processes will then constitute
138 secondary phenomena (Castano et al., 2005; Robertson et al., 2009).

139

140

141 **2.1.2. Sensitized photo-oxidations from T₁ triplet photosensitizer**

142 The PS triplet state T₁ is very reactive and presents two possible modes of interactions, either
143 directly with the molecules of the tissue where it is found, or with the molecular oxygen in the
144 triplet state (³O₂) (endogenous and exogenous) present in the media. Consequently, there are
145 two types of reactions for this stage, type I and type II reactions (Foote, 1991).

146

147 **2.1.2.1. Type I reaction**

148 In this case, PS in the triplet state generates radicals that react directly with O-containing
149 substrates basically by electron transfer. This process leads to the production of ROS (OH[•],
150 H₂O₂ ...). One of the most common reaction uses molecular oxygen as a substrate affording
151 superoxide anion radical (O₂^{•-}). The initiated cascade of reactions leads to the oxidative stress
152 resulting in the destruction of cancer cells (Braun et al., 1986; Kwiatkowski et al., 2018;
153 Luksiene, 2003; Nowak-Stepniowska et al., 2013).

154

155 **2.1.2.2. Type II reaction**

156 In this case, the PS in the triplet state T₁ will transfer its energy to an oxygen molecule that
157 will pass from the fundamental state triplet ³O₂ to the excited singlet state ¹O₂ (Braun et al.,
158 1986; Nowak-Stepniowska et al., 2013). The singlet oxygen formed ¹O₂ will then interact
159 with different electron-rich organic molecules that will oxidize and cause damage to the
160 organelles of the cell such as the plasma membrane, mitochondria, lysosomes and nucleus,
161 giving rise to tumor necrosis (Dougherty et al., 1998; Kirakci et al., 2019).

162 In conclusion, PS and light are the initiating agents of a series of various chemical reactions
163 resulting in the production of oxygenated free radicals leading to the tumor destruction. To
164 fight against this photo-oxidation and the increase in oxidant compounds, the cell has several
165 defenses to maintain the $O_2^{\circ-}$ level and to prevent its conversion to OH° , such as superoxide
166 dismutase enzyme (SOD) that will eliminate $O_2^{\circ-}$ to form H_2O_2 and O_2 . Catalase, an enzyme
167 localized in peroxisomes catalyzes disproportionation of H_2O_2 to O_2 and H_2O . Likewise,
168 glutathione peroxidase, an enzyme present in mitochondria and in the cytosol of cells reduces
169 H_2O_2 and organic peroxides formed (Ochsner, 1997). However, if SOD is stable when facing
170 photosensitization, glutathione peroxidase and catalase are much less stable and will be
171 greatly degraded allowing an increase of oxidizing agents in the cell and therefore its gradual
172 destruction (Castano et al., 2005).

173

174 **3. Mechanisms of cell photo-destruction**

175 PDT is therefore based on several elements such as tumor area previously charged with PS,
176 photons exposure, PS activation, production of reactive oxygen species and concentration in
177 molecular oxygen. These ROS are responsible for cell destruction by the following
178 mechanisms.

179

180 **3.1. Role of singlet oxygen**

181 Singlet oxygen 1O_2 is formed by the combined action of a PS, light and oxygen; It is a
182 powerful oxidant which reacts with many cellular components such as membrane
183 (phospholipid bilayer and cholesterol), amino acids (histidine, tryptophan, and methionine)
184 and nucleic bases (guanine). Due to its very short lifetime (0.01 to 0.04 μs) and its high
185 reactivity, 1O_2 acts directly on tumor area and does not have time to diffuse further off-sites
186 (Vrouenraets et al., 2003).

187 Photo-cytotoxic activity will therefore depend on several factors:

- 188 - quantum yields of S_1 state formation
- 189 - conversion yields from S_1 to T_1
- 190 - efficiency of energy transfer from PS T_1 state to 3O_2
- 191 - PS localization and subcellular concentration

192 PS used in PDT have the ability to focus mostly in tumor cells (Dellinger, 1996; Dos Santos
193 et al., 2019), this seems to come from tumor with larger permeable neo-blood vessels and an
194 increase in the number of LDL (Low Density Lipoproteins) receptors. PS are usually small
195 molecules, but they are bind to plasma LDL and therefore react like macromolecules which
196 can then bind to larger receptors number in tumor cells (Cruz et al., 2013).

197 The destruction of tumor cells is done by photodestruction following direct mechanisms such
198 as necrosis or apoptosis or indirect mechanisms such as vascular damage or immune response
199 (Kessel, 2019; Kessel and Oleinick, 2018, 2010).

200

201 **3.2. Direct mechanisms**

202 The direct cellular photodestruction mechanisms combine two categories, necrosis and
203 apoptosis. This direct cell damage depends on factors such as the dose, the location of the PS
204 in the cell and the cell line.

205

206 **3.2.1. Necrosis**

207 Necrosis is a non-programmed death cell. In PDT, this cellular reaction is caused by ROS
208 (type I reaction) and by singlet oxygen (type II reaction). Necrosis leads to an increase of
209 permeability and a loss of integrity for cell membranes. The cellular content also diffuses into
210 the surrounding tissues causing inflammatory reactions (Kessel and Oleinick, 2018).

211

212 **3.2.2. Apoptosis**

213 Apoptosis or programmed cell death, is a normal programmed cellular mechanism for which
214 cells self-destruct in response to a signal. This phenomenon results in the death of individual
215 cells, in certain places, at a specific time. The body uses apoptosis mechanism to get rid of
216 unusable, unwanted, or potentially harmful cells. When using PDT, ROS and singlet oxygen
217 can cause mitochondrial apoptosis or "death receptors" by activating caspases proteins
218 (Kessel, 2019).

219

220 **3.3. Indirect mechanisms**

221 These mechanisms of indirect cellular damages include targeted reactions to tumor vascular
222 tissue as well as inflammatory responses and immune systems.

223

224 **3.3.1. Indirect damages to the tumor vascular tissue**

225 As PS are mainly hydrophobic, they bind to plasma LDL and therefore accumulate at the
226 level of LDL receptors in the proliferating endothelial tissue in the case of tumor tissue. With
227 this accumulation in the neo-vessels and after PS activation, vascular damage occurs around
228 the tumor causing cells death by oxygen and nutrients depletion (Huang et al., 2008;
229 Krammer, 2001).

230

231 **3.3.2. Indirect damages due to inflammation and the immune response**

232 When activated PS makes damages to tumor cells, there is a release of inflammatory
233 mediators. A local inflammatory reaction occurs with an influx of neutrophils, mast cells,
234 monocytes and macrophages. Subsequently these macrophages can serve as antigen
235 presenting cells recognized by lymphocytes which opens the way for immunologic therapy or
236 even the possibility of on-site vaccination (Castano et al., 2006; Reginato et al., 2014).

237

238 **4. Photosensitive materials**

239 The choice of PS is very important to allow an effective photosensitization. Thus, the
240 photosensitizing compound must meet the following general criteria (Braun et al., 1986;
241 Kwiatkowski et al., 2018):

- 242 - the absorption domain of the PS must be located in the visible or UV and must
243 imperatively be located in a spectral region where the compound to be oxidized does
244 not absorb, to avoid unwanted side reactions.
- 245 - the PS must be inert towards oxygen singlet $^1\text{O}_2$ and compounds to be oxidized so it
246 will not participate in photochemical reactions.
- 247 - the energy of the T_1 triplet state of the PS must be greater than that of singlet oxygen
248 $^1\text{O}_2$ so that the transfer energy is efficient.
- 249 - the lifetime of the T_1 triplet state must be long enough to allow a good interaction
250 between the PS and oxygen in the triplet state $^3\text{O}_2$.
- 251 - the quantum yield of the conversion from S_1 to T_1 (ϕ) must be the largest possible to
252 allow good stand of T_1 triplet state thus allowing other deactivation processes to be of
253 minor importance.

254 Whatever the type of PS, these conditions must be respected in order to allow an effective
255 PDT. In addition to these requirements, the products used in PDT must have certain properties
256 more specific to photochemotherapy such as few side effects and a specificity oriented
257 towards type II reaction generating singlet oxygen and therefore ROS. Currently, PS can be
258 classified into three generations (Kwiatkowski et al., 2018).

259

260 **4.1. Classification of photosensitizers**

261 **4.1.1. First generation photosensitizers**

262 In the 1960's, Schwartz developed a mix based on hematoporphyrin (Hp) and derivatives
263 (Davis and Schwartz, 1967; Modell and Schwartz, 1964a, 1964b; Sternberg et al., 1998). This
264 preparation, whose composition was often variable, was called hematoporphyrin derivatives.
265 Lipson and Baldes have used hematoporphyrin derivatives in combination with other
266 porphyrins, protoporphyrin (PpIX) and uroporphyrin and their irradiation with light to treat
267 breast cancer successfully. This was really the beginning of photochemotherapy based on the
268 use of porphyrins (Lipson and Baldes, 1960). At the end of the 20th century, various
269 preparations of hematoporphyrin derivatives have been used in many clinical trials. In 1998,
270 Sternberg *et al.* developed Photofrin II[®], an ultrafiltrate of hematoporphyrin derivatives
271 (Sternberg et al., 1998). Subsequently, the Canadian QLT laboratories synthesized Photofrin[®],
272 a mixture resulting from numerous purifications and considered as the gold standard of PDT.
273 Photofrin[®] is the trade name of porfimer sodium which is a mixture of oligomers forming
274 dimers and trimers connected by ester or ether bonds. The determination of the active fraction
275 of this product was not easy, many works and studies were conducted for this purpose
276 (Tsukagoshi, 1995).

277 It seems that only the dimers and trimers with ether bonds are exhibiting effective
278 photocytotoxic activity, as ester bonds are instable under physiological conditions (Pandey et
279 al., 1988). In addition, ether bonds are destroyed in acidic media like tumor pH, it is therefore
280 probable that these ether-bridged dimers are cleaved into monomers when they enter the
281 tumor cells (Pandey et al., 1990).

282 Although Photofrin[®] has effective photocytotoxicity, it also exposes to certain limits such as:

- 283 - a strong accumulation in the skin causing important side effects up to six weeks after
284 treatment.

285 - an absorption and photoactivation wavelength near 630 nm, the wavelength range at
286 which endogenous tissues chromophores in particular oxyhemoglobin will also absorb
287 light thus reducing Photofrin[®] photoactivation. In addition, light scattering within the
288 tissue will also limit Photofrin[®] tissular penetration (Miller, 1999).

289
290 These limits of Photofrin[®] led to the numerous works and studies to discover new PS
291 products from the 1980's. One of the objectives of this research is to find compounds
292 absorbing at wavelengths in the red or even in the near infrared to avoid interference
293 mentioned above and to improve the penetration of light into the cancerous matrix therefore
294 extending PDT to deeper tumor treatments.

295

296 **4.1.2. Second generation photosensitizers**

297 Second generation PS have been developed to overcome the disadvantages of
298 hematoporphyrin derivatives. These synthetic molecules, with a defined chemical structure,
299 have an optimized light absorption spectrum allowing biggest size tumors treatment, but have
300 no selectivity towards tumor cells. Several compounds have obtained a marketing approval or
301 are currently being evaluated. They are activated with a light at a wavelength between 600
302 and 800 nm, allowing an increase in the light penetration depth in the tissue. Besides, these
303 are pure compounds, quickly eliminated by tissues, thus limiting the period of skin
304 photosensitization (Nowak-Stepniowska et al., 2013). Currently, the second generation
305 photosensitizers group includes 5-aminolevulinic acid (Effala[®], Ameluz[®], Gliolan[®],
306 Alacare[®]) (Fukuhara et al., 2020), methyl-aminolevulinate (Metvix[®], Metvixia[®]), meso-
307 tetrahydroxyphenylchlorin (Foscan[®]) (Posadzki and Car, 2018), benzoporphyrine derivatives
308 (Visudyne[®]) (Di Nicola et al., 2020), rostoporfin (Purlytin[®]) (Hunt, 2002), padeliporfin
309 (Tookad[®]) (Fukuhara et al., 2020), mono-L-aspartylchlorine e6 (Laserphyrin[®], Aptocine[®])

310 (Aizawa et al., 1987), phthalocyanines (Rak et al., 2019), lutetium texaphyrin (Lutex[®],
311 Lutrin[®]) (Young et al., 1996), lutetium motexafin (Antrin[®]) (Chen et al., 2001), gadolinium
312 motexafin (Xcytrin[®]) (Evens, 2004), methylene blue (Dos Santos et al., 2017) and rose bengal
313 (Dini et al., 2010).

314

315 **4.1.3. Third generation photosensitizers**

316 Second generation PS are not very specific for tumor cells, which is a limiting factor for the
317 implementation of an effective and selective PDT. Several studies were performed to develop
318 vectorized PS using chemical species recognized specifically by one type of tumor cell. One
319 of the axis of research on new PS consists in coupling a PS already synthesized with
320 monoclonal antibodies to enhance PS affinity for the tumor cells and therefore to improve
321 targeting while reducing side effects. For example, there are studies on new modified
322 texaphyrins (Arambula et al., 2011; Preihs et al., 2013), new vectors by chemical coupling
323 with small peptides (Johnson et al., 2014, 2013), estradiol-derived groups (El-Akra et al.,
324 2006),...

325 All cellular pathways expand targeting and uptake of PS by receptor-target interaction. The
326 main research lines focus on PS glycoconjugated, glycosylated or conjugated with estradiol to
327 improve active targeting of tumor cells, for example the targeting of estrogen receptor alpha
328 (Swamy et al., 2006). Another line of research is studying passive targeting of tumor cells by
329 vectorization of PS using liposomes, nanoparticles (NPs) as well as emulsions or micelles,
330 allowing PS to reach tumors at much higher concentrations (Chen et al., 2001; Dollo et al.,
331 2020; Evens, 2004; Rak et al., 2019; Young et al., 1996).

332

333 **4.1.4. Inorganic photosensitizers**

334 Among new PS currently studied we can cite nano-sized metal clusters, aggregates of atoms
335 of transition metals interconnected by metal-metal bonds like hafnium (Liu et al., 2016),
336 niobium (Ivanov et al., 2020) or molybdenum (Jackson et al., 1996). In particular,
337 hexanuclear molybdenum halide cluster complexes with the general formula $(\text{Mo}_6\text{L}^a_8\text{L}^i_6)^{2-}$,
338 L^a =halogen; L^i =halogen or organic ligands (Fig. 3) have been widely studied due to their
339 photo-physical and photo-chemical properties (Kirakci et al., 2018, 2012; Solovieva et al.,
340 2016). They have interesting optical, magnetic, electrical and catalytic properties currently
341 used in many fields such as electronics (as insulators or metallic conductors) but also have
342 interesting potential for biotechnology and nanotechnology (optics, imaging, and
343 theranostics). This combination of a drug and a diagnostic test is called theranostics (Lee et
344 al., 2012). Indeed, their possibility of generating singlet oxygen after activation is a real
345 advantage.

346 **4.2. Current clinical applications**

347 PDT has reached its climax in the 1980's when multiple clinical teams, primarily in the
348 United States, Canada and Japan, have shown its effectiveness in destroying usually
349 inoperable tumors (Dougherty, 1984). However, despite marketing authorizations
350 (Photofrin®, 1997; Foscan®, 2002), clinical sites using these techniques are unusual. Among
351 the reasons advanced we can cite the lack of knowledge of pathologies eligible for PDT.
352 However, companies continue to invest in this area and we can mention the launching on the
353 market of methyl-aminolevulinate (Metvixia®) and 5-aminolevulinic acid (Effala®) in
354 dermatology (Pariser et al., 2003). In ophthalmology, PDT using benzoporphyrine derivatives
355 (Visudyne®) experienced a strong enthusiasm in treatment of patients with neovascular form
356 (still called wet or exudative and characterized by an abnormal growth of blood vessels) of
357 age-related macular degeneration (Brown et al., 2005). However, since 2006, intravitreal

358 injections of bevacizumab (Avastin[®]), a humanized monoclonal antibody with anti-
359 angiogenic activity, have dramatically reduced the use of PDT.

360 In urology, the French company Steba-Biotech has developed a new PS, padeliporfin
361 (Tookad[®]) for the treatment of prostate cancer (Azzouzi et al., 2013). Computer-controlled
362 planning combined with real-time dosimetry is an essential research route to facilitate
363 application, reduce local toxicity and increase anticancer efficacy. However, the concept of
364 partial treatment or focal therapy for prostate cancer is recent and still controversial in the
365 urological community due to the frequency of tumor multifocality. If the functional results of
366 the first clinical trials are encouraging, evidence of long-term cancer efficacy is pending.

367 In gastroenterology, PDT benefits from a renewed interest due to the development of diode
368 lasers (which advantageously replace the first dye lasers pumped by argon laser) and to the
369 demonstration of its effectiveness i) for the treatment of superficial esophageal cancers in
370 patients inaccessible to another treatment, with a post-radiotherapy recurrence (Wu et al.,
371 2019), ii) for severe dysplasia in Barrett's mucosa (Panjehpour and Overholt, 2006), and iii)
372 for inoperable cholangiocarcinoma, with the aim of prolonging the survival of patients
373 receiving palliative biliary drainage (Gao et al., 2010).

374 In gynecology, the value of PDT was shown in the treatment of high grade cervical dysplastic
375 lesions after application of a 5-aminolevulinique acid solution (5-ALA) (Hillemanns et al.,
376 2014; Matoba et al., 2018). The PDT applied to the endometrium seems promising,
377 particularly in the treatment of functional menorrhagia in the premenopausal period. Use of a
378 local PDT after 5-ALA intra-uterine instillation has shown that this could be an alternative to
379 the surgical treatment currently offered.

380 In neurosurgery, several studies reported encouraging results in the clinic using interstitial
381 photodynamic therapy (iPDT) to treat first-line non-operable glioblastomas (brain tumors) or
382 their recurrences. Survivals greater than two years following iPDT have been reported while

383 the median survival in the event of recurrence is estimated to be three months (Beck et al.,
384 2007).

385 In pneumology, the number of studies on the treatment of lung cancer is still limited and the
386 place of PDT in therapeutic arsenal remains to be investigated (Moghissi and Dixon, 2003).

387 On the other hand, PDT appears to be a promising treatment for malignant pleural
388 mesothelioma (MPM) or primary cancers pleura. Thus, PDT has been tested in phase I and II
389 clinical trials for MPM patients in combination with extra-pleural pneumonectomy or
390 pleurectomy/decortication followed by intravenous chemotherapy. The first work carried out
391 by Professor Friedberg's team (University of Pennsylvania, Philadelphia, USA) has shown
392 promising results with median overall survival 31 months (Du et al., 2010).

393 In dermatology, PDT is gradually becoming the standard treatment for actinic keratosis
394 (precancerous skin lesions), basal cell carcinomas superficial and Bowen's disease (intra-
395 epidermal cancer, *in situ*). It is efficient, relatively easy to perform (although progress is
396 expected on the sources of light), well tolerated and inexpensive, generating no aesthetic
397 consequences. In the literature, response rates up to 90% are reported for PDT of actinic
398 keratosis treatment (Morton et al., 2013). The growing interest in this technique is confirmed
399 by the recent marketing of products competing with methyl-aminolevulinate (Metvix[®]), such
400 as 5-aminolevulinic acid (Ameluz[®]) developed by the Biofrontera company (Reinhold et al.,
401 2016). The different drugs actually on the market for photodynamic therapy is presented
402 (Table. 1).

403

404 **5. Areas of improvement for PDT**

405 **5.1. Irradiation improvement**

406 **5.1.1. Biphotonic excitation**

407 The use of a classic PDT excitement, i.e. based on the excitation of the PS by absorption of a
408 photon has the drawback of requiring the use of excitation wavelengths located most often in
409 the visible, which results in a low penetration of light into the tissues, i.e. less than 5 mm. The
410 spectral window operable in biological media is between 700 and 1100 nm due to the weaker
411 diffusion in this area and also the lower absorbance of biomolecules such as melanin,
412 hemoglobin and water. Two photons excitation PDT (2PE-PDT) can be interesting to excite a
413 PS with classic activation in the visible with two processes, i.e. two-photon absorption (TPA)
414 and up-conversion (Sivasubramanian et al., 2019). TPA is a nonlinear optics phenomenon
415 based on simultaneous absorption of two lower energy photons (and therefore of longer
416 wavelength) to lead to the excited state (He et al., 2008). This TPA approach has also shown
417 its interest in studies carried out *in vivo* (Collins et al., 2008). The advantages of this
418 technique compared to the classic PDT results in a better light penetration in a biological
419 environment and an important spatial selectivity, minimizing the risk of accidental destruction
420 of healthy tissue. It is however necessary to rationally design new PS with sufficiently large
421 TPA cross section, having good solubility in biological aqueous media, good photostability
422 and safety in the absence of light and ability to cross biological membranes. The molecular
423 two-photon cross-section $\sigma^{(2)}$ is usually quoted in of Goepfert-Mayer unit (GM) where 1 GM
424 is $10^{-50} \text{ cm}^4 \cdot \text{s} \cdot \text{photon}^{-1}$, resulting from the product of two areas (one for each photon, each in
425 cm^2) and a time (within which the two photons must arrive to be able to act together).

426 Recent studies have demonstrated the potential of supramolecular buildings based on
427 porphyrins, leading to huge $\sigma^{(2)}$ values, typically of several orders of magnitude greater than
428 those of the former PS. Arena-Ru (II) complexes have shown their potential interest in the
429 treatment of cancers and metastasis (Scolaro et al., 2005), where Ru (II) polypyridyl
430 complexes have attracted great attention as potential PS in PDT. Their stability and chemical
431 inertness in solution, possible engineering for the modularity of their photophysical properties

432 such as TPA, as well as the relatively long shelf life of their excited state triplet MLCT
433 (Metal-to-Ligand Charge Transfer) (Girardot et al., 2007) give them clear advantages as
434 potential PS in excited two-photon PDT. Furthermore, hybridized functionalized silica
435 nanoparticles by molecular PS presenting strong TPA responses were also developed. These
436 nano-objects have demonstrated strong potential *in vivo*, in two photon excitation PDT (Gary-
437 Bobo et al., 2011).

438

439 **5.1.2. X-ray excitation**

440 Nanoparticles can take advantage of their physical and chemical particular properties to
441 envisage an innovative therapeutic strategy which can combine PDT and radiotherapy via the
442 use of nanoparticulate scintillators excitable by X-rays (Kamkaew et al., 2016). The concept
443 consists in using scintillator loaded nanoparticles which, excited by X-rays, can in turn emit
444 photons reabsorbed by the PS itself, grafted onto the NP matrix. It is therefore no longer
445 necessary to use an external light source to generate the photodynamic effect. This concept
446 was demonstrated by Chen and Zhang in 2006 (Chen and Zhang, 2006). Recent publications
447 show that this kind of nanoscintillators allows to consider the use of nanoparticles for PDT,
448 excitable by radiotherapy (Sun et al., 2020). Recently, a new generation of inorganic PS based
449 on octahedral molybdenum cluster complexes have proven their ability to produce ROS after
450 exposure to X-rays (Kirakci et al., 2018). This feature eliminates energy losses during energy
451 transfer from the scintillating nanoparticles to the surrounding PS occurring in the original
452 systems (Chen and Zhang, 2006), and considerably simplifies the PS architecture. Upon
453 excitation with light, they form long-lived triplet states that relax via red-NIR luminescence.
454 In another recent application, Kirakci et al. showed that for a new water-soluble molybdenum
455 cluster complex with iodine inner ligands and carboxylated apical ligands bearing ethylene
456 oxide groups, the X-ray-induced toxicity on cancer cells as well as the *in vivo* toxicity were

457 low or moderate, confirming the pertinence of octahedral molybdenum cluster complexes as
458 singlet oxygen radiosensitizers for X-PDT (Kirakci et al., 2021). These findings could be a
459 source of considerable ramifications in the treatment of cancers.

460

461 **5.2. Nanotechnology**

462 A major challenge in cancer therapy is to override body's defense mechanisms to bring the
463 drug to its biological target (Sanhai et al., 2008). The question is to limit non-specific effects
464 while ensuring a high concentration in the tumor. Some compounds are under investigation,
465 obtained by conjugation of a PS to a tumor addressing molecule (sugars, peptides and
466 ligands). However, one of major issue for PS remains their hydrophobicity which promotes
467 aggregation in biological media and limits their bioavailability. One solution could be to
468 encapsulate the PS in nanoparticles to improve its bioavailability (Shi et al., 2017). They have
469 the advantage of increasing PS penetration in tissues and cells as well as the efficacy of PDT
470 (Mallidi et al., 2016). It is also possible to combine a PS and a labeling agent within the same
471 nanoparticles. Nanovector systems, which ensure good drug protection and targeting, are
472 among the most relevant candidates to become the future generation of anti-cancer vectors
473 (Zhao et al., 2020). Liposomes are an effective vectorization strategy for PDT (Derycke and
474 de Witte, 2004). However, these synthetic vectors must be designed very carefully to
475 overcome biocompatibility issues of the carrier and protection of the drug. Ratajczak *et al.*
476 developed a strategy using cell microvesicles as a platform for transport. After their isolation,
477 PS are loaded in these vesicles by co-incubation using different concentration gradient. In the
478 case of hydrophobic compounds, the internalization could be reached by a simple passive
479 diffusion process (Susa et al., 2019). The idea is to take advantage of a natural transportation
480 system to design a biogenic nanovector, i.e. a cell-derived nanovector. These microvesicles,
481 naturally released by most cells under physiological conditions or under the effect of different

482 stimuli, circulate freely in the organism where they act as natural carrier of cellular material.
483 PS can use these intercellular taxis to travel from one cell to another (Ratajczak et al., 2006),
484 thus internalized by cells, they can come out through these microvesicles, which will then be
485 picked up by other cells. It is also possible to co-internalize PS and magnetic NPs, making of
486 these microvesicles true multifunctional vectors capable of being detected by MRI (Magnetic
487 Resonance Imaging) and manipulated or guided by magnetic forces and following release into
488 tumor cells, to couple PDT and treatment by magnetic hyperthermia. This type of stealth
489 nanoplatform is therefore part of a theranostic anticancer approach (Silva et al., 2015).

490 Preliminary studies for the formulation and evaluation of NPs of organic copolymer of lactic
491 and glycolic acid (PLGA) containing several inorganic molybdenum clusters have been
492 carried out (Brandhonneur et al., 2018; Dollo et al., 2020). PLGA nanoparticles containing
493 $\text{Mo}_6\text{I}_8 (\text{OCOC}_2\text{F}_5)_6$ cluster (CMIF) in the form of cesium salt were prepared by a solvent
494 displacement technique. Cell viability was evaluated *in vitro* on the A2780 ovarian cancer cell
495 line after treatment by the free or encapsulated cluster in NPs for concentrations varying from
496 5 to 100 $\mu\text{g} / \text{ml}$ and for different incubation times (24, 48 and 72h). A strong photo-toxicity
497 was obtained for CMIF loaded nanoparticles with a half maximal inhibitory concentration
498 (IC_{50}) value near 1.8 μM (Brandhonneur et al., 2020). Preliminary work therefore presents the
499 octahedral clusters of molybdenum as new PS for PDT of ovarian cancer and suggest that
500 PLGA polymer nanoparticles constitute a delivery system suitable for targeting cells tumor.
501 Additionally, Vorotnikov et al. used targeting antibodies C7b and trastuzumab for grafting of
502 Mo_6 -containing silica nanoparticles for *in vivo* photodynamic treatment of cancer on
503 xenografted mice (Vorotnikov et al., 2020).

504

505 **Conclusion**

506 Many second or third generation photosensitizers are cited in the literature, but very few are
507 approved for clinical use. The most recent developments are oriented towards the design and
508 study of PS targeted towards several cancers according to their biological characteristics. A
509 second line of research, in full swing, consists in selectively destroying the neo-vessels
510 supplying nutrients to the tumor in order to eradicate them by privation of energy or oxygen
511 resources. One of the only real drawbacks of PDT is the low penetration of light in the tissues
512 as well as the relatively low specificity of this method. However, ways of improvement are in
513 development (X-ray, nanosystems ...). In conclusion, the combination of nanotechnology and
514 new inorganic PS is a promising technique to optimize PDT treatment of tumors.

515

516

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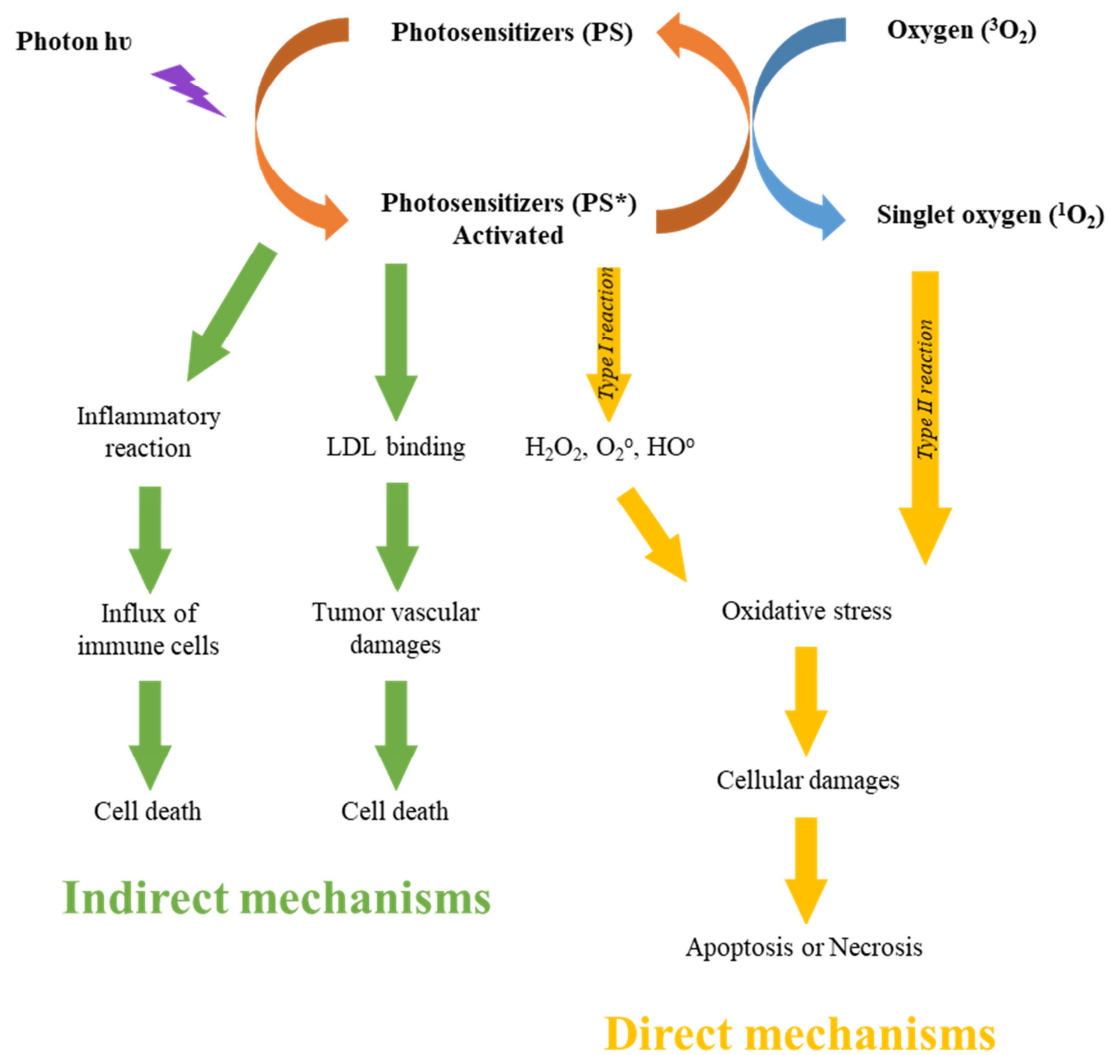
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843

844 **Table 1:** Summary of the different drugs on the market for photodynamic therapy. EMA: European Medicine Agency, FDA: U.S. Food and Drug
 845 Administration, MHLW: Japanese Ministry of Health, Labour and Welfare. (*): drug withdrawn from the market

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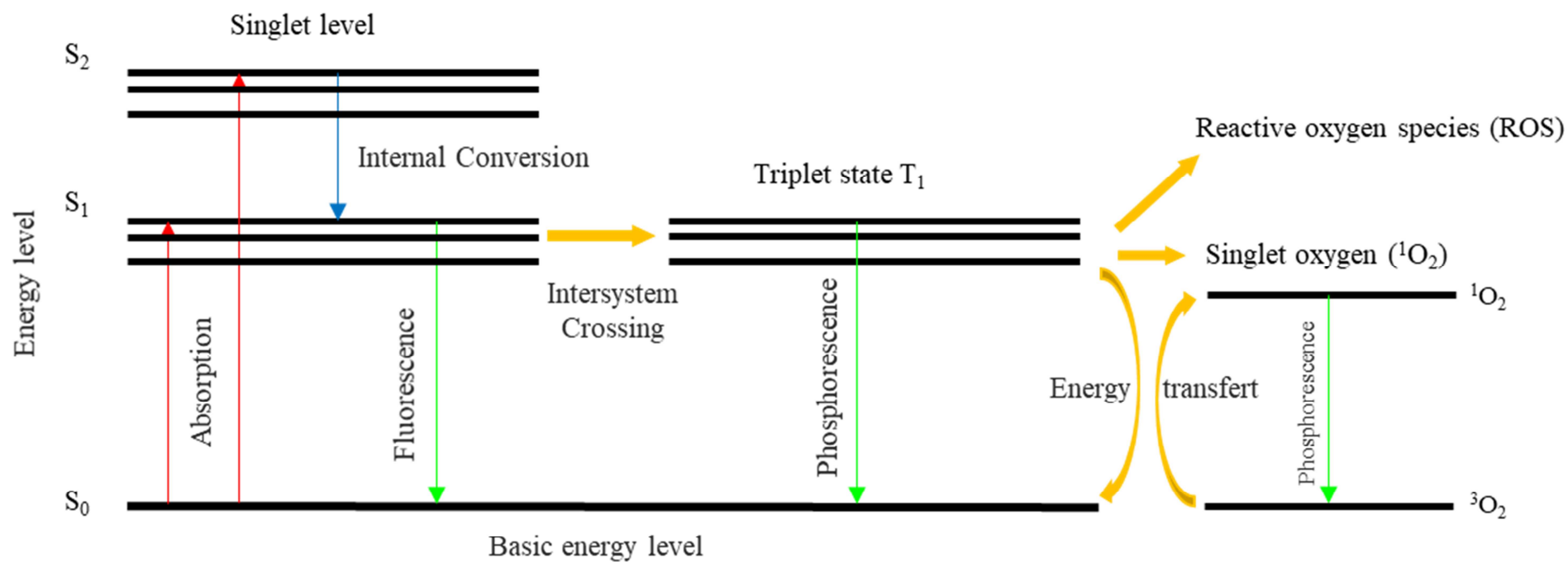
Photosensitizers	Classification of photosensitizer	Proprietary Names and Owner	Pharmaceutical form	Marketing authorisation	Pathology
Porfirmer Sodium	First generation	Photobarr [®] (Pinnacle)	injectable solution	2004 (EMA)*	Lung and esophageal cancer
		Photofrin [®] (Axcan)	injectable solution	2003 (FDA)	
5-Aminolevulinic Acid	Second generation	Alacare [®] (Galderma)	medicated plaster	2011 (EMA)	Moderate actinic keratosis, basal cell carcinoma
		Ameluz [®] (Biofrontera)	gel	2011 (EMA) 1999 (FDA)	
		Effala [®] (Galderma)	medicated plaster	2011 (EMA)	
		Gliolan [®] (Medac)	powder for oral solution	2007 (EMA) 1999 (FDA)	Malignant glioma
Hexaminolevulinic Hydrochloride		Hexvix [®] (Ipsen)	powder for intravesical solution	2013 (EMA) 2010 (FDA)	Diagnosis of bladder cancer, Treatment of cervical dysplasia
Methyl-aminolevulinic		Metvix [®] (Galderma)	cream	2011 (EMA)	Moderate actinic keratosis, basal cell carcinoma
		Metvixia [®] (Galderma)	cream	2011 (EMA) 2004 (FDA)	
Meso-tetrahydroxyphenylchlorin (temoporfin)		Foscan [®] (Biolitec Pharma)	injectable solution	2001 (EMA)	Advanced head and neck squamous cell carcinoma
Verteporfin		Visudyne [®] (QLT)	powder for injectable solution	2000 (EMA) 2002 (FDA)	“Wet” form of age-related macular degeneration (AMD), choroidal neovascularisation caused by pathologic myopia
Padeliporfin		Tookad [®] (STEBA Biotech)	powder for injectable solution	2017 (EMA)	Prostate cancer
Mono-L-aspartylchlorine e6 (Talaporfin)	Laserphyrin [®] (Meiji Seika)	injectable solution	2004 (MHLW)	Early-stage lung cancer	



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848 **Figure 1.** Mechanism of the photodynamic reaction and biological effects

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851 **Figure 2.** Modified Jablonski diagram showing the formation of singlet oxygen.

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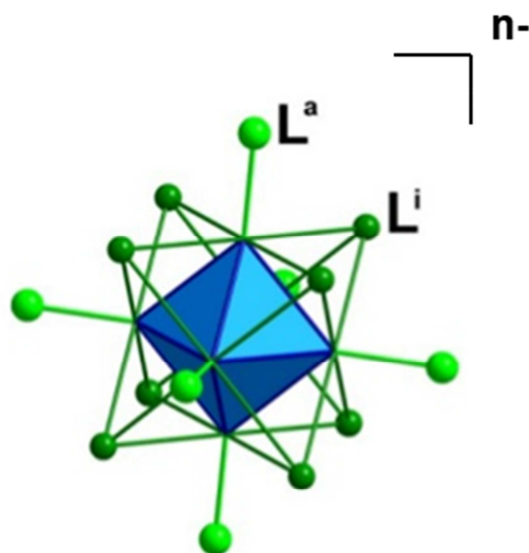
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861 **Figure 3.** General structure of hexanuclear molybdenum halide cluster unit ($Mo_6L^i_8L^a_6$) where L^i and L^a represent inner and apical ligands
 862 respectively and A^+ represents the counter cation, from (Dollo et al., 2020)

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