



Singlet oxygen-activatable Paclitaxel prodrugs via intermolecular activation for combined PDT and chemotherapy

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ABSTRACT

Systemic side effects and high hydrophobicity are major disadvantages of paclitaxel (PTX), one of the most popular anticancer drugs. Here, we present singlet oxygen (SO)-activatable and mitochondria-targeted PTX prodrugs to overcome these problems and boost the cytotoxic effect of photodynamic therapy (PDT). Three PTX prodrugs were prepared by conjugating PTX with various cationic groups. Hydrophobicity was determined in LogD_{7.4} value. Mitochondrial localization was confirmed by fluorescence confocal microscopy and uptake of mitochondria-specific fluorescence probe. Dark- and photo-toxicity were measured in AY-27 cells with MTT assay. All three prodrugs showed better hydrophilicity than PTX and improved phototoxicity when combined with protoporphyrin IX (PpIX) PDT. In conclusion, SO-activatable and higher hydrophilic PTX prodrugs were successfully prepared. This approach could be used to improve the antitumor efficacy of PDT without the systemic side effects of PTX.

Paclitaxel (PTX) is a widely used first-line treatment option for various cancers, including breast cancer,^{1,2} ovarian cancer,^{3–5} and non-small-cell lung cancer.⁶ Adjuvant and neoadjuvant systemic chemotherapy are typical uses of PTX.^{7–11} The mechanism of PTX is to stabilize microtubule assembly through interaction with tubulin. This process results in the inhibition of cellular growth by blockage of cell replication in the late G2 mitotic phase of the cell cycle.^{12–17} Despite its common use in cancer treatments, hydrophobicity and systemic side effects remain major challenges.^{18–23} Hence, the quest for selective delivery of PTX to cancer cells to minimize non-specific toxicity and the hydrophobicity of PTX is of great interest.

Photodynamic therapy (PDT) is a FDA-approved treatment modality for a number of cancers, including bladder, lung, and esophageal cancers.^{24–27} The photodynamic effect is due to the formation of reactive oxygen species under light illumination of photosensitizers.²⁸ However, PDT still presents the challenge of recurrence due to cells surviving after PDT,^{29–30} partly due to the short half-life (~10–320 ns) and limited diffusion distance (~10–55 nm) of singlet oxygen (SO) in cells.^{31,32} The FDA approved HAL (hexyl-5-aminolevulinic acid) for fluorescent diagnosis of non-muscle invasive bladder cancer (NMIBC) in 2010.^{33,34} The selective accumulation of protoporphyrin IX (PpIX) in the mitochondria of cancer cells via HAL has been well validated.^{35,36} The

conversion of HAL to PpIX in the mitochondria of cancer cells enhances the selectivity of PpIX PDT, which can help to mitigate collateral damage to surrounding normal cells. However, the potency of PpIX PDT itself was not sufficient to eradicate NMIBC.³⁶

We recently demonstrated a novel intermolecular photo-unclick chemistry in the mitochondria, using a mitochondria-specific photosensitizer, PpIX, and SO-cleavable combretastatin A4 (CA4) prodrug.³⁷ CA4 and rhodamine (mitochondria targeting vector) were conjugated with an SO-cleavable linker. HAL was incubated with cancer cells to produce PpIX in the mitochondria.^{35,36} Upon visible light illumination, SO was generated by PpIX. The SO directly damaged the cancer cells (PDT effect) and initiated the cleavage of the SO-cleavable linker, subsequently causing the release of the active drug CA4.

Herein, our goals were to prepare visible light-activatable and mitochondria-targeted prodrugs of PTX (Fig. 1) by conjugating PTX with mitochondrial targeting vectors via an aminoacrylate linker (SO-cleavable linker), and to evaluate their mitochondriotropic properties and *in vitro* phototoxic activity improving the effects of PpIX PDT.

We prepared Rh-*l*-PTX, CAT-*l*-PTX, and TPP-*l*-PTX by conjugating PTX to three mitochondriotropic lipophilic cations (MLCs), rhodamine (Rh), 4-carboxy-1-methylpyridinium chloride (CAT), triphenylphosphonium (TPP), respectively, via a SO-labile aminoacrylate linker (*l*)

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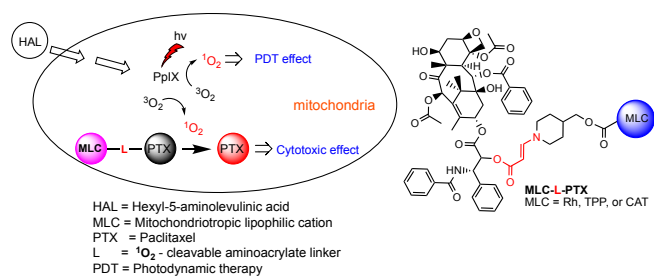
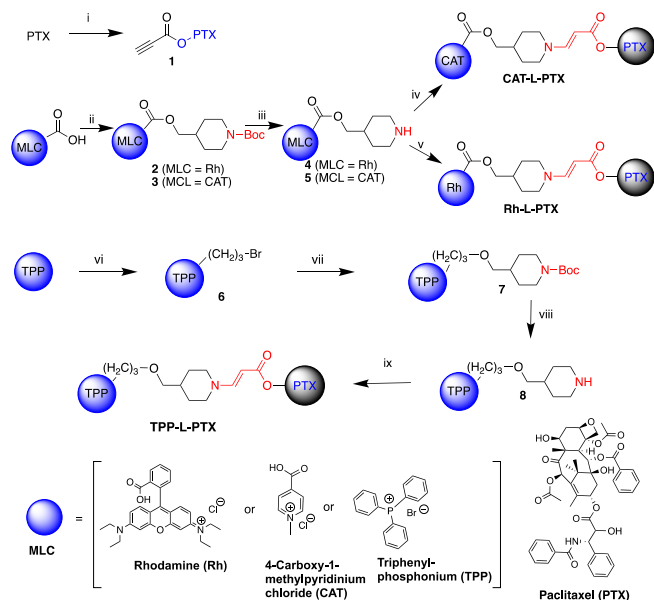


Fig. 1. Mitochondriotropic PTX prodrugs for a light-activatable combination of PDT and site-specific chemotherapy. PTX prodrugs targeted to mitochondria for more effective activation by SO generated in mitochondria.



Scheme 1. Synthesis of Rh-L-PTX, TPP-L-PTX, and CAT-L-PTX; reagents and conditions: (i) 2-propynoic acid, DCC, DMAP, anhydrous DCM, rt, 24 h, 74%; (ii) *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate, DCC, DMAP, anhydrous DCM, 24 h, 78% (2) and 75% (3); (iii) TFA, anhydrous DCM, rt, 1 h; (iv) 1, *N*, *N*-diisopropylethylamine, DMF, rt, 1 h, 87%; (v) 1, *N*, *N*-diisopropylethylamine, THF, rt, 1 h, 86%; (vi) 1,3-bromopropane, toluene, reflux, 18 h, 80%; (vii) *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate, anhydrous K_2CO_3 , anhydrous DMF, rt, 12 h, 76%; (viii) TFA, anhydrous DCM, rt, 1 h; (ix) 1, *N*, *N*-diisopropylethylamine, DMSO, 40 °C, 5 h, 35%.

(Scheme 1). All three prodrugs were readily prepared via simple, easy, and high to moderate-yielding reactions, such as esterification, yne-amine, nucleophilic substitution, and amidation. PTX, rhodamine, and CAT were esterified using DCC and DMAP to give compounds 1, 2, and 3, respectively. Rh-L-PTX and CAT-L-PTX were synthesized via a click chemistry (yne-amine reaction) of compound 1 with compound 4 and 5 in 84% and 87% yield, respectively. Compound 6 was synthesized by nucleophilic substitution of TPP and 3-bromopropan-1-ol. TPP-L-PTX was synthesized via a click reaction (yne-amine reaction) of compounds 8 and 1 in 35% yield. The relatively low yield of TPP-L-PTX may be due differences in solubility of compounds 8 and 1.

We chose Rh and TPP groups because both are well-known mitochondriotropic targeting vectors (delocalizing lipophilic cations).^{39–42} The CAT group was chosen due to its small molecular size and its positive charge as a mitochondriotropic lipophilic cation (Table 1).⁴³ LogD_{7.4} values were determined by the modified shake flask method.⁴⁴ All three prodrugs were more hydrophilic than was PTX itself: LogD_{7.4} = 3.6 (PTX) vs. 1.9–1.0 (prodrugs) (Table 1). CAT-L-PTX had the highest hydrophilicity (logD_{7.4} = 1.0) and smallest molecular weight (1176 g/mole) among the three prodrugs.

Table 1

Molecular characters of PTX and mitochondriotropic prodrugs.

Number	Name	MW (g/mole)	Charge	LogD _{7.4}
1	PTX	854	0	3.6 ³⁸
2	Rh-L-PTX	1482	1	1.9
3	CAT-L-PTX	1176	1	1.0
4	TPP-L-PTX	1404	1	1.3

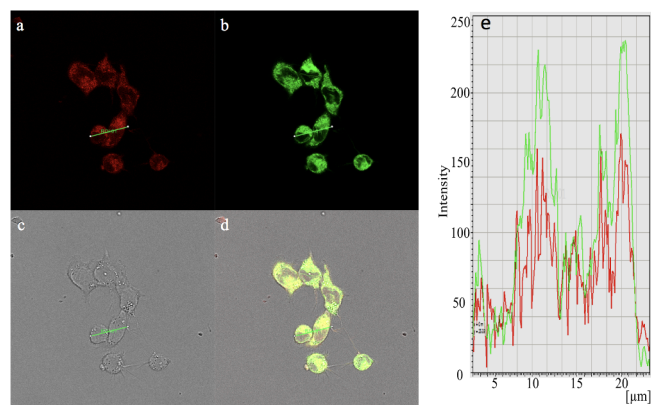


Fig. 2. Dual staining with Rh-L-PTX and MDR, 0.5 μM each after incubation for 30 min. a) channel for Rh-L-PTX (ext. 561 nm and em. 570–630 nm), b) channel for MDR (ext. 633 and em. 650–700 nm), c) bright field, and d) overlap of a, b, and c. e) Relative fluorescence intensity across the line for Rh-L-PTX and MDR channels.

To confirm the mitochondrial localization, we used fluorescence dual staining with mitochondrial membrane probe, MDR [MitoTracker Deep Red] for Rh-L-PTX and PpIX. Since the other two prodrugs do not emit fluorescence, we could not confirm their mitochondrial localization. Taking advantage of the Rh fluorescence emission of Rh-L-PTX (em. max. = 590 nm), dual staining with MDR (em. max. = 665 nm) was performed (Fig. 2) with AY-27 rat bladder carcinoma cells. Rh-L-PTX showed typical mitochondrial localization pattern in the cells, overlapping well with those of MDR (Fig. 2d and e). Since PpIX is generated via HAL, mitochondrial localization of PpIX in AY-27 cells was examined. AY-27 cells were incubated with HAL for 2 h. The AY-27 cells were excited at 410 nm, and the fluorescence emission of PpIX (em. max. = 630 nm) was observed (Fig. 3). The subcellular localization of PpIX showed the typical mitochondrial pattern in cells and overlapped well with those of MDR (Fig. 3d and e).

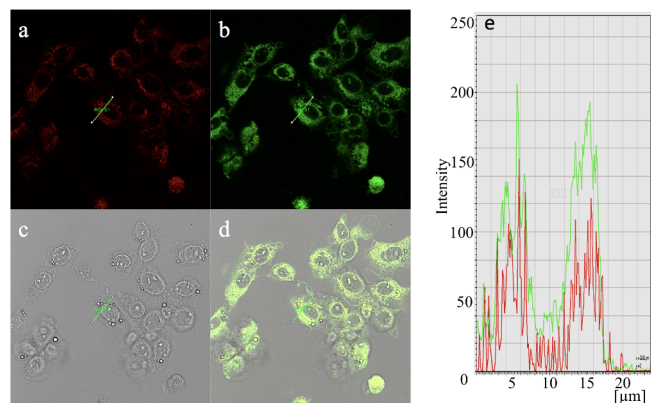


Fig. 3. Dual staining with PpIX (formed by 0.5 mM HAL) and 0.5 μM MDR after incubation for 30 min. a) channel for PpIX (ext. 410 nm and em. 620–700 nm), b) channel for MDR (ext. 633 and em. 650–700 nm), c) bright field, and d) overlap of a, b, and c. e) Relative fluorescence intensity across the line for PpIX and MDR channels.

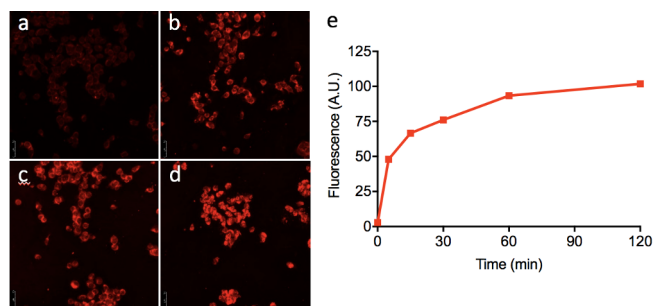


Fig. 4. (a–d) Time-dependent fluorescence images with 1 μM Rh-L-PTX for 5, 30, 60, and 120 min incubation, channel for Rh (ext. 540–580 nm, em. 592–668 nm), (e) Cellular uptake of Rh-L-PTX after 5, 15, 30, 60, and 120 min incubation at 5 μM .

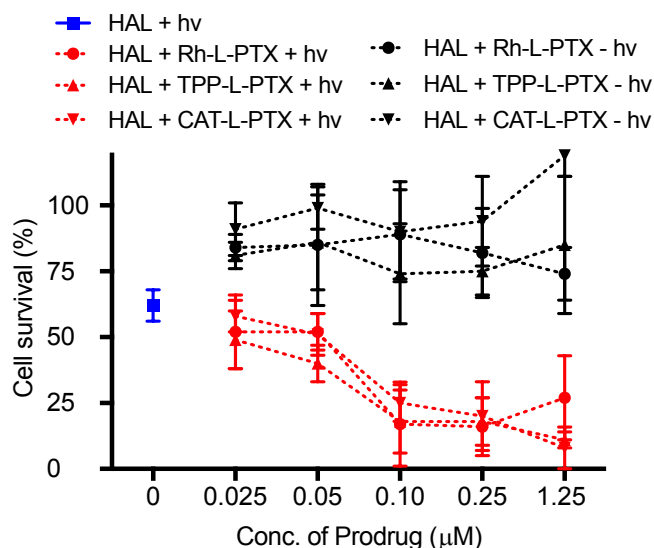


Fig. 5. Cytotoxic effect of PpIX PDT (HAL⁺ + hv), HAL⁺ + Rh-L-PTX (or TPP-L-PTX, or CAT-L-PTX) without illumination, and PpIX PDT + Rh-L-PTX (or TPP-L-PTX or CAT-L-PTX) with illumination (531 nm at 10 mW/cm² for 30 min); *HAL at 0.5 mM for 2 h.

Time-dependent uptake of Rh-L-PTX was determined using fluorescence microscopy (Fig. 4a–d) and a plate reader (Fig. 4e) after incubation for 5, 30, 60, and 120 min. Rh-L-PTX showed rapid uptake with saturation at ~ 60 min. At 120 min incubation with 5 μM , ~ 0.68 fmole/cell was achieved, which should be sufficient to achieve a cytotoxic intracellular concentration of PTX (e.g., IC₅₀ = ~ 0.02 fmole/cell)⁴⁵ after $> 90\%$ activation of the prodrug by SO generated by PpIX PDT.³⁷ One of the potential applications of these prodrugs is for treating NMIBCs to enhance the phototoxicity of PpIX PDT. The prodrug and HAL could be instilled in a bladder and then illuminated with visible light (e.g., 532 nm). In such an application, maximum instillation time is limited to ~ 2 h. A sufficient amount of prodrug should be taken up by cancer cells in 2 h.

Cellular survival of three groups [(1) PpIX PDT (HAL (0.5 mM) + hv), (2) dark- (HAL + prodrug – hv), and (3) phototoxicity (HAL + prodrug + hv) of a mixture of HAL (0.5 mM) and a series of concentrations (0.025–1.25 μM) of the three prodrugs] was determined (hv = 531 nm diode laser, 10 mW/cm², 30 min) (Fig. 5). PpIX PDT killed about $\sim 40\%$ of the cells. Even at the highest concentration of prodrugs (1.25 μM) with HAL, no significant cytotoxicity was observed without illumination. In stark contrast, upon illumination, approximately 84%, 82%, and 80% of cells were killed with 0.25 μM Rh-L-PTX, TPP-L-PTX, and CAT-L-PTX, respectively. The higher phototoxicity of these groups compared with PpIX PDT ($\sim 40\%$ cell kill) could be

attributed to PTX released from the SO-activated prodrugs. PTX release from aminoacrylate linker (L)-tethered PTX prodrug (Pc-(L-PTX)₂) by SO was demonstrated in our previous report.⁴⁶ Without HAL, no significant photo or dark toxicity was observed by the prodrugs (Figs. S6–S8).

In conclusion, we designed mitochondriotropic and SO-activatable prodrugs of PTX for combined chemo-photodynamic therapy via intermolecular activation. Three novel PTX prodrugs were synthesized using a facile synthetic scheme with mild reaction conditions and high yields. All prodrugs showed higher hydrophilicity than PTX itself. The enhanced phototoxicity of PpIX PDT by the addition of these PTX prodrugs might be due to the released PTX inside the cancer cells. This is the first demonstration of mitochondriotropic and SO-activatable PTX prodrugs via the intermolecular activation mechanism, potentiating PpIX PDT. Combination of chemotherapy and phototherapy in various forms is emerging for improved antitumor effect and lowered off-target toxicity.^{47–49}

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Appendix A. Supplementary data

Electronic Supplementary Information (ESI) available: synthesis of the compounds, NMR.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bmcl.2019.03.053>.

References

- Crown J, O'Leary M, Ooi WS. Docetaxel and paclitaxel in the treatment of breast cancer: a review of clinical experience. *Oncologist*. 2004;9:24–32.
- Gennari A, Guarneri V, Landucci E, et al. Weekly docetaxel/paclitaxel in pretreated metastatic breast cancer. *Clin Breast Cancer*. 2002;3(5):346–352.
- Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2003;21(17):3194–3200.
- Kampan NC, Madondo MT, McNally OM, Quinn M, Plebanski M. Paclitaxel and Its evolving role in the management of ovarian cancer. *Biomed Res Int*. 2015;2015 Article ID 413076, 21 pages.
- Kumar A, Hoskins PJ, Tinker AV. Dose-dense paclitaxel in advanced ovarian cancer. *Clin Oncol-Uk*. 2015;27(1):40–47.
- Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol*. 2012;30(17):2055–2062.
- Burness ML, Obeid EI, Olopade OI. Triple negative breast cancer in BRCA1 mutation carriers with a complete radiologic response to neoadjuvant paclitaxel: a case report. *Clin Breast Cancer*. 2015;15(2):e155–e158.
- Glasgow MA, Yu H, Rutherford TJ, et al. Neoadjuvant chemotherapy (NACT) is an effective way of managing elderly women with advanced stage ovarian cancer (FIGO Stage IIIC and IV). *J Surg Oncol*. 2013;107(2):195–200.
- Okazawa M, Masuhara K, Miyoshi A, et al. A rare case of ovarian carcinosarcoma successfully treated with the neoadjuvant chemotherapy of paclitaxel and ifosfamide. *J Obstet Gynaecol*. 2011;31(3):274–275.
- Horiguchi J, Oyama T, Koibuchi Y, et al. Neoadjuvant weekly paclitaxel with and without trastuzumab in locally advanced or metastatic breast cancer. *Anticancer Res*. 2009;29(2):517–524.
- Palumbo R, Sottotetti F, Trifiro G, et al. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) as second-line chemotherapy in HER2-negative, taxane-pretreated metastatic breast cancer patients: prospective evaluation of activity, safety, and quality of life. *Breast Des Dev Ther*. 2015;9:2189–2199.
- Horwitz SB. Mechanism of action of taxol. *Trends Pharmacol Sci*. 1992;13(4):134–136.
- Sparano JA, Wang ML, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *New Engl J Med*. 2008;358(16):1663–1671.

14. Montana M, Ducros C, Verhaeghe P, Terme T, Vanelle P, Rathelot P. Albumin-bound paclitaxel: the benefit of this new formulation in the treatment of various cancers. *J Chemotherapy*. 2011;23(2):59–66.
15. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *New Engl J Med*. 2006;355(24):2542–2550.
16. Zhan M, Tao WY, Pan SH, Sun XY, Jiang HC. Low-dose metronomic chemotherapy of paclitaxel synergizes with cetuximab to suppress human colon cancer xenografts. *Anti-Cancer Drug*. 2009;20(5):355–363.
17. Gill PS, Tulpule A, Espina BM, et al. Paclitaxel is safe and effective in the treatment of advanced AIDS-related Kaposi's sarcoma. *J Clin Oncol*. 1999;17(6):1876–1883.
18. Peltier S, Oger JM, Lagarce F, Couet W, Benoit JP. Enhanced oral paclitaxel bioavailability after administration of paclitaxel-loaded lipid nanocapsules. *Pharm Res*. 2006;23(6):1243–1250.
19. Zhang YC, Benet LZ. The gut as a barrier to drug absorption – Combined role of cytochrome P450 3A and P-glycoprotein. *Clin Pharmacokinet*. 2001;40(3):159–168.
20. Cresteil T, Monsarrat B, Alvinerie P, Treluyer JM, Vieira I, Wright M. Taxol metabolism by human liver-microsomes – identification of cytochrome-p450 isozymes involved in its biotransformation. *Cancer Res*. 1994;54(2):386–392.
21. Kumar GN, Walle UK, Walle T. Cytochrome-P450 3a-mediated human liver microsomal Taxol 6- α -hydroxylation. *J Pharmacol Exp Ther*. 1994;268(3):1160–1165.
22. Rahman A, Korzekwa KR, Grogan J, Gonzalez FJ, Harris JW. Selective Biotransformation of Taxol to 6- α -Hydroxytaxol by Human Cytochrome-P450 2c8. *Cancer Res*. 1994;54(21):5543–5546.
23. Sonnichsen DS, Liu Q, Schuetz EG, Schuetz JD, Pappo A, Relling MV. Variability in Human Cytochrome-P450 Paclitaxel Metabolism. *J Pharmacol Exp Ther*. 1995;275(2):566–575.
24. Stenzl A, Burger M, Fradet Y, et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. *J Urology*. 2010;184(5):1907–1913.
25. Bader MJ, Stepp H, Beyer W, et al. Photodynamic Therapy of Bladder Cancer – A Phase I Study Using Hexaminolevulinate (HAL). *Urol Oncol-Semin Ori*. 2013;31(7):1178–1183.
26. Simone CB, Friedberg JS, Glatstein E, et al. Photodynamic therapy for the treatment of non-small cell lung cancer. *J Thorac Dis*. 2012;4(1):63–75.
27. Lightdale CJ, Heier SK, Marcon NE, et al. Photodynamic Therapy with Porfimer Sodium Versus Thermal Ablation Therapy with Nd-Yag Laser for Palliation of Esophageal Cancer – a Multicenter Randomized Trial. *Gastrointest Endosc*. 1995;42(6):507–512.
28. Dougherty TJ. An update on photodynamic therapy applications. *J Clin Laser Med Surg*. 2002;20(1):3–7.
29. Wilson JJ, Jones H, Burock M, et al. Patterns of recurrence in patients treated with photodynamic therapy for intraperitoneal carcinomatosis and sarcomatosis. *Int J Oncol*. 2004;24(3):711–717.
30. Lindberg-Larsen R, Solvsten H, Kragballe K. Evaluation of recurrence after photodynamic therapy with topical methylaminolaevulinate for 157 basal cell carcinomas in 90 patients. *Acta Derm-Venerol*. 2012;92(2):144–147.
31. Dysart JS, Patterson MS. Characterization of Photofrin photobleaching for singlet oxygen dose estimation during photodynamic therapy of MLL cells in vitro. *Phys Med Biol*. 2005;50(11):2597–2616.
32. Agostinis P, Berg K, Cengel KA, et al. Photodynamic therapy of cancer: an update. *Ca-Cancer J Clin*. 2011;61(4):250–281.
33. Rink M, Babjuk M, Catto JWF, et al. Hexyl aminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: a critical review of the current literature. *Eur Urol*. 2013;64(4):624–638.
34. Witjes JA, Redorta JP, Jacqmin D, et al. Hexaminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: review of the evidence and recommendations. *Eur Urol*. 2010;57(4):607–614.
35. Berrahmoune S, Fotinos N, Bezdetnaya L, et al. Analysis of differential PDT effect in rat bladder tumor models according to concentrations of intravesical hexyl-aminolevulinate. *Photoch Photobio Sci*. 2008;7(9):1018–1024.
36. Cosserat-Gerardin I, Bezdetnaya L, Notter D, Vigneron C, Guillemin F. Biosynthesis and photodynamic efficacy of protoporphyrin IX (PpIX) generated by 5-aminolevulinic acid (ALA) or its hexylester (hALA) in rat bladder carcinoma cells. *J Photoch Photobio B*. 2000;59(1–3):72–79.
37. Bio M, Rajaputra P, Lim I, et al. Efficient activation of a visible light-activatable CA4 prodrug through intermolecular photo-unclick chemistry in mitochondria. *Chem Comm*. 2017;53(11):1884–1887.
38. Jauhari S, Singh Somnath, Dash AK. *Profiles of Drug Substances, Excipients and Related Methodology*. Waltham, MA, USA: Elsevier BV; 2009:299–344.
39. Modicanapolitano JS, Aprille JR. Basis for the selective cytotoxicity of rhodamine-123. *Cancer Res*. 1987;47(16):4361–4365.
40. James AM, Blaikie FH, Smith RA, Lightowlers RN, Smith PM, Murphy MP. Specific targeting of a DNA-alkylating reagent to mitochondria. Synthesis and characterization of [4-((11aS)-7-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-o n-8-oxy)butyl]-triphenylphosphonium iodide. *Eur J Biochem*. 2003;270(13):2827–2836.
41. Ngen EJ, Rajaputra P, You Y. Evaluation of delocalized lipophilic cationic dyes as delivery vehicles for photosensitizers to mitochondria. *Bioorgan Med Chem*. 2009;17(18):6631–6640.
42. Rajaputra P, Nkepan G, Watley R, You YJ. Synthesis and in vitro biological evaluation of lipophilic cation conjugated photosensitizers for targeting mitochondria. *Bioorgan Med Chem*. 2013;21(2):379–387.
43. Murphy MP, Smith RAJ. Targeting antioxidants to mitochondria by conjugation to lipophilic cations. *Annu Rev Pharmacol*. 2007;47:629–656.
44. Leo A, Hansch C, Elkins D. Partition coefficients and their uses. *Chem Rev*. 1971;71(6):525–+.
45. Li M, Thapa P, Rajaputra P, Bio M, Peer CJ, Figg WD, You Y, Woo S. Quantitative modeling of the dynamics and intracellular trafficking of far-red light-activatable prodrugs: implications in stimuli-responsive drug delivery system. *J Pharmacokinet Pharmacodyn*. 2017;44:521–536.
46. Thapa P, Li M, Bio M, et al. Far-red light-activatable prodrug of paclitaxel for the combined effects of photodynamic therapy and site-specific paclitaxel chemotherapy. *J Med Chem*. 2016;59:3204–3214.
47. Luo D, Carter KA, Miranda D, Lovell JF. Chemophototherapy: an emerging treatment option for solid tumors. *Adv Sci*. 2017;4:1600106.
48. Zhang Y, Feng L, Wang J, et al. Surfactant-stripped micelles of near infrared dye and paclitaxel for photoacoustic imaging guided photothermal-chemotherapy. *Small*. 2018;14:1802991.
49. Carter KA, Luo D, Geng J, Stern ST, Lovell JF. Blood interactions, pharmacokinetics, and depth- dependent ablation of rat mammary tumors with photoactivatable, liposomal doxorubicin. *Mol Cancer Ther*. 2019;18:592–601.