



Metal-based photosensitizers for photodynamic therapy: the future of multimodal oncology?

Sherri Mcfarland, Arkady Mandel, Roger Dumoulin-White, Gilles Gasser

► To cite this version:

Sherri Mcfarland, Arkady Mandel, Roger Dumoulin-White, Gilles Gasser. Metal-based photosensitizers for photodynamic therapy: the future of multimodal oncology?. *Current Opinion in Chemical Biology*, 2020, 56, pp.1900139. <10.1016/j.cbpa.2019.10.004>. <hal-02373926>

HAL Id: hal-02373926

<https://hal.science/hal-02373926v1>

Submitted on 26 Nov 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Metal-based Photosensitizers for Photodynamic Therapy: The Future of Multimodal Oncology?

Sherri A. McFarland,^{a,b,} Arkady Mandel,^c Roger Dumoulin-White,^c and Gilles Gasser^{d,*}*

- ^a The University of Texas at Arlington, Department of Chemistry and Biochemistry, Arlington, TX 76019-0065, USA. Email: sherri.mcfarland@uta.edu; WWW: https://www.uta.edu/chemistry/faculty/sherri_mcfarland.php
- ^b The University of North Carolina at Greensboro, Department of Chemistry and Biochemistry, Greensboro, NC 27402-6170, USA.
- ^c Theralase Technologies Inc., Toronto, Ontario, Canada, Email: amandel@theralase.com, rwhite@theralase.com, www.theralase.com
- ^d Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, Laboratory for Inorganic Chemical Biology, F-75005 Paris, France. Email: gilles.gasser@chimieparistech.psl.eu; WWW: www.gassergroup.com

ORCID-ID:

Sherri A. McFarland: 0000-0002-8028-5055

Gilles Gasser: 0000-0002-4244-5097

Abstract

Photo Dynamic Therapy (PDT) is an approved medical technique to treat certain forms of cancer. It has been used to complement traditional anticancer modalities such as surgery, chemotherapy or radiotherapy and in certain cases, to replace these treatments. One critical parameter of PDT is the Photo Sensitizer (PS); historically, a purely organic macrocyclic tetrapyrrole-based structure. This short review surveys two recent clinical examples of metal complexes, namely TOOKAD®-Soluble and TLD-1433, which have ideal photophysical properties to act as PDT PSs. We highlight the important role played by the metal ions in the PS for PDT activity.

Introduction

Cancer remains a leading cause of death worldwide despite notable advances in traditional anticancer modalities (i.e.: pharmaceutical drugs, surgery, chemotherapy, radiotherapy and more recently, immunotherapy). It is now recognized that multimodal strategies are the future of oncology, with many pharmaceutical companies pursuing alternative approaches or adjuvants to complement and increase the efficacy of existing therapies. Photo Dynamic therapy (PDT) has existed for over 100 years, albeit it in dramatically different forms. Recently, PDT has emerged as a medical intervention to treat certain types of cancer, that were unable to be treated by traditional means. PDT has also been used to remedy some skin conditions (i.e.: acne, port wine stains, etc.), fungal and microbial infections or age-related macular degeneration.[1-3]

PDT utilizes a Photo Sensitizer (PS), light and endogenous oxygen to destroy tumors and/or tumor vasculature, in addition to inducing an immune response.[4-11] It is delivered in a two-step procedure consisting of local or systemic administration of a PS, at a non-toxic dose, followed by light activation. PDT has the capacity to be highly selective with precise delivery of the light and/or preferential uptake of the PS by tumors. An important attribute of PDT is that toxicity is confined to regions where the three components overlap spatiotemporally.

The PDT effect stems from excitation of the PS to produce a singlet excited state that undergoes Inter System Crossing (ISC) to form the reactive triplet state. The triplet state then sensitizes cytotoxic singlet oxygen ($^1\text{O}_2$) through Type II energy transfer or participates in Type I electron transfer reactions to generate other Reactive Oxygen Species (ROS) such as superoxide or hydroxyl radicals. The Type II mechanism is accepted as the predominant pathway for most of the currently approved PSs. The relatively short lifetime and diffusion coefficient of $^1\text{O}_2$ estimated in biological environments is thought to limit its activity to a spherical radius of approximately 100 nm [12-14] or less.[15,16]

Photofrin® (Figure 1) is the only PS that was once approved worldwide for certain cancers (it has since been withdrawn from use in the European Union (EU). 5-Aminolevulinic acid (Levulan®)

and methyl 5-aminolevulinate (Metvix®), Protoporphyrin IX (PpIX) precursors, were later approved worldwide for basal cell carcinoma; except in the US, where they are approved for actinic keratosis (Figure 1). Only a handful of second and third generation PSs have been approved, and only in specific countries: temoporfin (Foscan®) in the EU, talaporfin (Laserphyrin®) in Japan, and LUZ111 (Redaporfin®) in the EU. Photosens®, Photodithazine®, Radachlorin® (also known as Bremachlorin® in the EU), and Photogem® have been approved in Russia.[17] Padeliporfin (WST11, TOOKAD® soluble) in Mexico, Israel, as well as in 31 countries of the EU and in the European Economic Area (EEA) (Figure 1).[10,18]

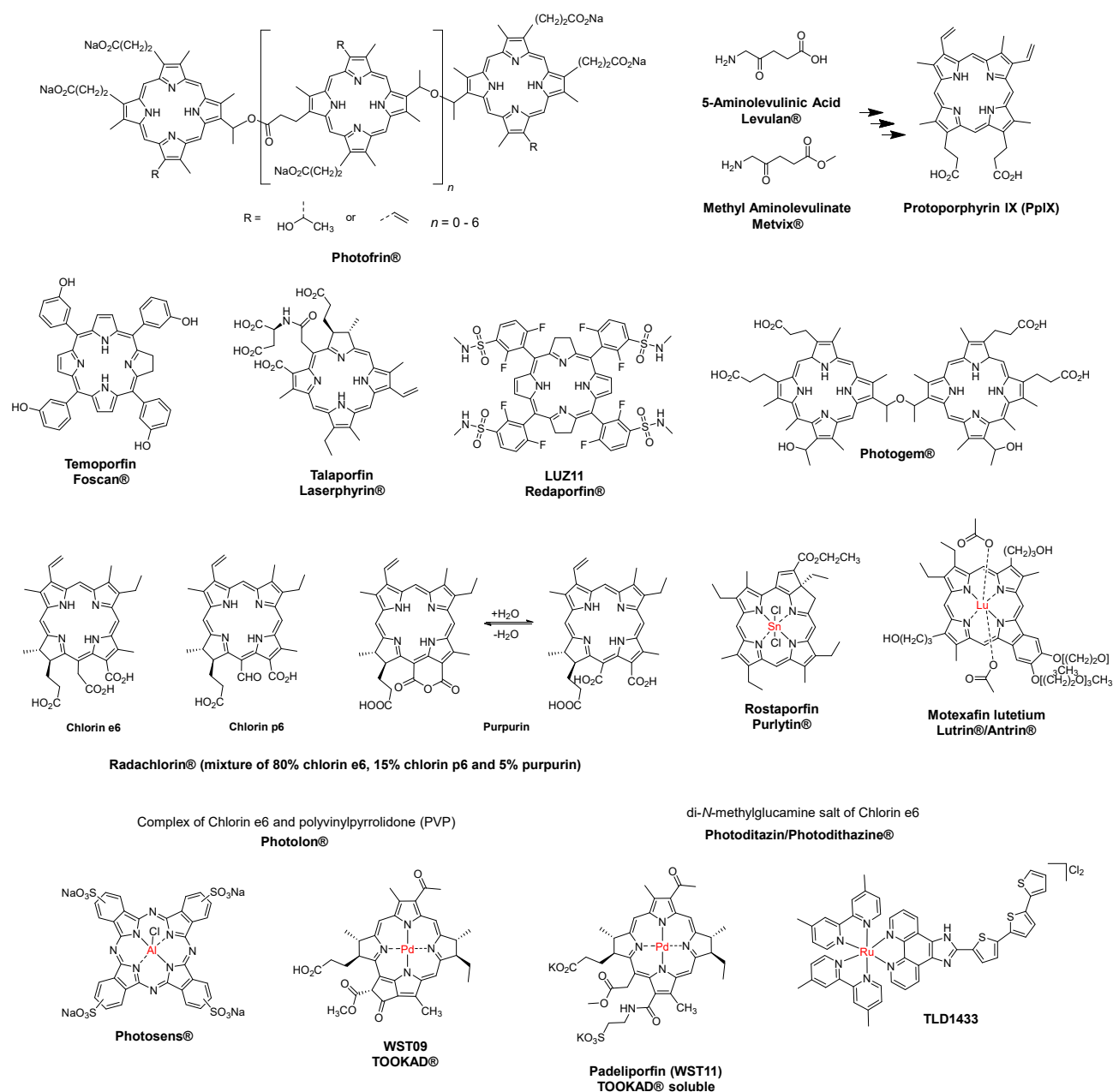


Figure 1. Structures of PSs approved or in clinical studies for oncologic PDT

While Photofrin set the standard for PDT, there is ongoing interest in developing the next-generation of PSs that address some limitations of the tetrapyrrolic systems. Single-agent, aqueous-soluble PSs that are prepared in high purity from straightforward syntheses are highly desirable. Low photobleaching rates, high selectivity for tumors, strong PDT effects with high irradiances and

favourable Pharmacokinetic (PK) properties for the intended application are additional considerations. Certain metal complexes have much to offer in this respect, and we anticipate that an increasing number will be investigated for PDT applications in the future.[10,19-27] To the best of our knowledge, only a few PSs containing metal ions have advanced to clinical studies. Photosens® (n= 1-4) and TOOKAD® soluble have been approved, while Purlytin®, Motexafin lutetium (Lutrin®/Antrin®), and TLD-1433 are under clinical investigation (Figure 1). In this contribution, we highlight the two recent clinical examples of metal-based PSs that have been investigated for oncologic PDT, namely TOOKAD® Soluble and TLD-1433, emphasizing the roles played by the metal ions in their observed activities.

TOOKAD® Soluble

TOOKAD® Soluble (Padeliporfin, WST11, Figure 1) from Steba biotech is the first and only palladium-based PS to be approved anywhere in the world and is currently being used to treat low-risk prostate cancer with Vascular Targeted PDT (VTP). It is a negatively-charged derivative of the photosynthetic pigment Bacteriochlorophyll α (Bchl), a molecule that certain bacteria use to produce energy from sunlight.[28] TOOKAD® Soluble was developed by Salomon, Scherz and co-workers in Israel and is the improved water-soluble version of their earlier PS WST09 (Figure 1). TOOKAD® Soluble was found to avoid the cardiovascular events and subclinical hepatotoxicity associated with WST09.[29,30] It forms a non-covalent complex with Human Serum Albumin (HSA)[31] and consequently stays in the plasma until clearance, making it an ideal PS for VTP.

While most PSs for PDT work via a Type II mechanism with production of $^1\text{O}_2$, TOOKAD® Soluble appears to function exclusively through Type I photoreactions, generating only superoxide ($\text{O}_2^{\cdot-}$) and hydroxyl radicals ($\text{OH}\cdot$).[31] The complex formed between TOOKAD® Soluble and HSA has the unique ability to act as a photocatalytic oxidoreductase, permitting about 15 cycles of electron transfer from HSA to molecular oxygen in solution.[31] While BChl can easily isomerize, it is subject to degradation and is poorly soluble in aqueous solutions. Metal incorporation into the macrocycle overcomes these drawbacks by changing the hydrophobicity, optical spectrum, redox potentials and overall reactivity of the metallated PS compared to free BChl.[32] Importantly, metallation also serves to stabilize the PS with no significant effects on its absorption profile[32] and increases the photodynamic activity of the PS.

VTP with TOOKAD® Soluble is indicated for patients with only one side of the prostate affected that are expected to survive for at least 10 years.[18] TOOKAD® Soluble is injected intravenously over 10 minutes at a dose of 4 mg/kg. This injection is quickly followed by illumination of the zone to be treated with a 753-nm laser light at an average power density of 150 mW/cm² and laser light energy density of 200 J/cm² applied over 22 minutes and 15 seconds. The laser light is

delivered by very thin optical fibers that are inserted directly into the cancerous prostate tissue guided by ultrasound.[18,33] The burst of ROS produces rapid occlusion and destruction of the blood vessels, blocking blood and nutrient supply to the tumor.[34] This initial insult is followed by a series of events such as: thrombosis, blood stasis and vessel occlusion, leading finally to tumor necrosis.[34]

VTP with TOOKAD® Soluble was approved in certain countries following the results of a randomized phase III clinical trial (47 European university centres and community hospitals) that included 206 patients receiving treatment compared to 207 patients on active surveillance.[35] All patients were men with low-risk localised prostate cancer. The study concluded that TOOKAD® Soluble was a safe and effective treatment for low-risk, localised prostate cancer.[35] After 24 months, only 28% of the men in the treatment group had disease progression compared to 58% in the active surveillance group. Impressively, 49% of the treated men had a negative prostate biopsy result 24 months post VTP, while only 14% of the men in the active surveillance group had this same result.

TLD-1433

TLD-1433, or $[\text{Ru}(4,4'\text{-dmb})_2(\text{IP-3T})]\text{Cl}_2$ (4,4'-dmb=4,4'-dimethyl-2,2'-bipyridine; IP=imidazo[4,5-*f*][1,10]phenanthroline; 3T= α -terthienyl, Figure 1), is the first ruthenium-based PS to advance to clinical studies and is being investigated to treat Non-Muscle Invasive Bladder Cancer (NMIBC) with PDT. It is a non-macrocyclic, non-pyrrolic metal coordination complex that is unique in its activity and photosensitizing mechanism. TLD-1433 utilizes an essential Ru(II) center to promote fast and efficient ISC to form triplet excited states with almost unity efficiency. The 3T chromophore installs thienyl-localized intraligand (^3IL)/intraligand charge transfer ($^3\text{ILCT}$) triplet excited states of significant $\pi\pi^*$ character that have prolonged excited state lifetimes. These states sensitize $^1\text{O}_2$ in very high yield and can also participate in electron transfer reactions.[10,19,36] Both of these aspects distinguish TLD-1433 from other Ru(II) complexes as well as from the free IP-3T ligand.

The highly photosensitizing $^3\text{IL}/^3\text{ILCT}$ states can be accessed indirectly with green laser light or populated directly with red laser light. The phototoxic effects with green laser light are very potent and this shorter wavelength is crucial for treating tumors with a steep PDT dose gradient to prevent damage to underlying healthy tissue. Because TLD-1433 selectively accumulates in bladder cancer cells, whole bladder illumination with intravesical delivery of both the PS and laser light is possible. Intravesical delivery, activation of the PS with shorter-wavelength green light (520 nm), and in situ, real-time optical dose monitoring to achieve uniform delivery of the desired irradiance and fluence at the inner bladder surface are unique features of this treatment procedure.

The general protocol involves administration of TLD-1433 directly into the bladder, intravesically through a catheter, for approximately 60 minutes to allow time for accumulation of the PS in bladder tumors. This is followed by bladder voiding and washing with sterile water to remove any excess TLD-1433 not localized to bladder cancer cells and finally an instillation of sterile water to distend the bladder and facilitate uniform light distribution. This leads to a Drug-to-Light Interval (DLI) of approximately 90 minutes. An optical fiber with a spherical diffuser is then inserted into the

geometric center of the bladder and 520 nm laser light is delivered until a total fluence of approximately 90 J/cm² is delivered to the inner bladder wall. Exposure times are approximately 1 to 1.5 hours, but vary based on the bladder volume and hence the bladder surface area. The irradiance delivered to the bladder wall is monitored via a detector array (surrounding the spherical diffuser) equipped with irradiance sensors positioned symmetrically on the bladder wall. The sensors provide real-time feedback on the irradiance and radiant exposure at the bladder wall, which allows the urologist to more precisely determine when the desired laser light energy density has been achieved.

TLD-1433 has already completed a Phase Ib, open-label, single-arm, single-center clinical study (n=9) sponsored by Theralase Technologies, Inc. (Toronto, Ontario, Canada) on patients with high-risk NMIBC that previously failed Bacillus Calmette Guérin (BCG) therapy and were not considered candidates for (or refused) radical cystectomy. This was a 3+6 clinical study, where 3 patients were treated at the Maximum Recommended Starting Dose (MRSD) (0.35 mg/cm²), followed by up to 3 patients treated at the Therapeutic Dose (0.70 mg/cm²). The primary (safety and tolerability), secondary (PK), and exploratory (efficacy) objectives of the study were all successfully achieved, after only 6 patients. Notably 67% of the patients in the Therapeutic Dose group demonstrated a Complete Response (“CR”): no presence, recurrence or progression of their bladder cancer, as evaluated by cystoscopy and urine cytology, 18 months after a single PDT treatment with TLD-1433. The clinical study was deemed a success and the sponsor terminated the study early, at the recommendation of the Medical and Scientific Advisory Board (MSAB), in order to proceed to a phase II clinical study with a primary objective of efficacy.

The phase II clinical study (www.clinicaltrials.gov, identifier NCT03945162) commenced in September 2019 and is planned to enrol and treat approximately 100 to 125 NMIBC patients (approximately 20 Canadian and US sites) that present with Carcinoma In-Situ (CIS), who are considered BCG-unresponsive or are intolerant to BCG therapy, with a primary objective of efficacy, as measured by CR at any point in time. A secondary objective of duration of CR, measured by CR 360

days post initial PDT and a tertiary objective of safety, measured by Adverse Events (AEs) that are ≥ 4 , that do not resolve within 360 days post initial PDT. These patients will receive two optimized PDT treatments (Day 0 and Day 180). It is anticipated that the study will take approximately two to three years to complete.

Conclusions and Perspectives

As demonstrated with two concrete examples in this short review, metal complexes will undoubtedly play an important role as PDT PSs in the future. We can expect a rise in the number of metal-based compounds entering clinical studies, not only as PDT agents, but also in other fields of medicine such as imaging and therapeutic agents. The potential approval of TLD-1433 in the coming years may pave the way for clinical investigation of other Ru(II) based complexes, which have remained in preclinical stages for a protracted time. We hope that the pharmaceutical industry will be less reticent to finance such expensive studies, due to the success of a compound of the same family.

Acknowledgments

This work was financially supported by: an ERC Consolidator Grant PhotoMedMet to G.G. (GA 681679) and has received support under the program *Investissements d'Avenir* launched by the French Government and implemented by the ANR with the reference ANR-10-IDEX-0001-02 PSL (G.G.), the University of North Carolina at Greensboro, The University of Texas at Arlington, the National Cancer Institute of the National Institutes of Health under Award Number R01CA222227 to S.A.M. and Theralase Technologies Inc. (Toronto, Ontario, Canada). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclaimer

Theralase licenses the exclusive worldwide rights for TLD-1433 and its associated PDCs.

References and recommended reading

• Papers of special interest

1. Kostron H, Hasan T: *Photodynamic medicine: From bench to clinic*. Royal Society of Chemistry, Cambridge, UK (2016).
2. Bonnett R: *Chemical aspects of photodynamic therapy*. Gordon and Breach Science Publishers, London and Newark (2000).
3. Henderson BW, Dougherty TJ: *Photodynamic therapy: Basic principles and clinical applications*. CRC Press, (1992).
4. van Straten D, Mashayekhi V, de Bruijn HS, Oliveira S, Robinson DJ: **Oncologic photodynamic therapy: Basic principles, current clinical status and future directions**. *Cancers* (2017) **9**(2).
5. Abrahamse H, Hamblin MR: **New photosensitizers for photodynamic therapy**. *Biochem J* (2016) **473**(4):347-364.
6. Agostinis P, Berg K, Cengel KA, Foster TH, Girotti AW, Gollnick SO, Hahn SM, Hamblin MR, Juzeniene A, Kessel D, Korbelik M *et al*: **Photodynamic therapy of cancer: An update**. *CA Cancer J Clin* (2011) **61**(4):250-281.
7. Dougherty TJ, Gomer CJ, Henderson BW, Jori G, Kessel D, Korbelik M, Moan J, Peng Q: **Photodynamic therapy**. *J Nat Cancer Inst* (1998) **90**(12):889-905.
8. Plaetzer K, Krammer B, Berlanda J, Berr F, Kiesslich T: **Photophysics and photochemistry of photodynamic therapy: Fundamental aspects**. *Laser Med Sci* (2009) **24**(2):259–268.
9. Allison RR: **Photodynamic therapy: Oncologic horizons**. *Future Oncol* (2014) **10**(1):123-124.
10. • Monro S, Colón KL, Yin H, Roque J, Konda P, Gujar S, Thummel RP, Lilge L, Cameron CG, McFarland SA: **Transition metal complexes and photodynamic therapy from a tumor-centered approach: Challenges, opportunities, and highlights from the development of TLD-1433**. *Chem Rev* (2019) **119**(797–828 and references therein).
11. Benov L: **Photodynamic therapy: Current status and future directions**. *Med Princ Pract* (2015) **24**(14-28).
12. Hatz S, Lambert JDC, Ogilby PR: **Measuring the lifetime of singlet oxygen in a single cell: Addressing the issue of cell viability**. *Photochem Photobiol Sci* (2007) **6**(10):1106-1116.

13. Hatz S, Poulsen L, Ogilby PR: **Time-resolved singlet oxygen phosphorescence measurements from photosensitized experiments in single cells: Effects of oxygen diffusion and oxygen concentration.** *Photochem Photobiol* (2008) **84**(5):1284-1290.
14. Ogilby PR: **Singlet oxygen: There is indeed something new under the sun.** *Chem Soc Rev* (2010) **39**(3181–3209
15. Moan J, Berg K: **The photodegradation of porphyrins in cells can be used to estimate the lifetime of singlet oxygen.** *Photochem Photobiol* (1991) **53**(4):549-553.
16. Moan J: **On the diffusion length of singlet oxygen in cells and tissues.** *J Photochem Photobiol B* (1990) **6**(3):343-344.
17. <https://doi.org/10.24931/2413-9432-2015-4-1-3-10>
18. https://ec.europa.eu/health/documents/community-register/2017/20171110139127/anx_139127_en.pdf
19. Shi G, Monro S, R. H, Colpitts J, Fong J, Kasimova K, Yin H, DeCoste R, Spencer C, Chamberlain L, Mandel A *et al*: **Ru(II) dyads derived from α -oligothiophenes: A new class of potent and versatile photosensitizers for PDT.** *Coord Chem Rev* (2014) **282-283**(127–138 and references therein.
20. • Heinemann FW, Karges J, Gasser G: **Critical overview of the use of Ru(II) polypyridyl complexes as photosensitizers in one-photon and two-photon photodynamic therapy.** *Acc Chem Res* (2017) **50**(2727-2736
21. Jakubaszek M, Goud B, Ferrari S, Gasser G: **Mechanisms of action of Ru(II) polypyridyl complexes in living cells upon light irradiation.** *Chem Commun* (2018) **54**(93):13040-13059, and references therein.
22. Chen Y, Guan R, Zhang C, Huang J, Ji L, Chao H: **Two-photon luminescent metal complexes for bioimaging and cancer phototherapy.** *Coord Chem Rev* (2016) **310**(16-40.
23. Zeng L, Gupta P, Chen Y, Wang E, Ji L, Chao H, Chen Z-S: **The development of anticancer ruthenium(II) complexes: From single molecule compounds to nanomaterials.** *Chem Soc Rev* (2017) **46**(19):5771-5804.
24. Mari C, Pierroz V, Ferrari S, Gasser G: **Combination of Ru(II) complexes and light: New frontiers in cancer therapy.** *Chem Sci* (2015) **6**(2660-2686.

25. • McKenzie LK, Bryant HE, Weinstein JA: **Transition metal complexes as photosensitisers in one- and two-photon photodynamic therapy.** *Coord Chem Rev* (2019) **379**(2-29).
26. Josefsen LB, Boyle RW: **Photodynamic therapy and the development of metal-based photosensitisers.** *Metal-based Drugs* (2008) **2008**(276109-276109).
27. • Poynton FE, Bright SA, Blasco S, Williams DC, Kelly JM, Gunnlaugsson T: **The development of ruthenium(II) polypyridyl complexes and conjugates for in vitro cellular and in vivo applications.** *Chem Soc Rev* (2017) **46**(24):7706-7756.
28. Mazor O, Brandis A, Plaks V, Neumark E, Rosenbach-Belkin V, Salomon Y, Scherz A: **Wst11, a novel water-soluble bacteriochlorophyll derivative; cellular uptake, pharmacokinetics, biodistribution and vascular-targeted photodynamic activity using melanoma tumors as a model.** *Photochem Photobiol* (2005) **81**(2):342-351.
29. Arumainayagam N, Moore CM, Ahmed HU, Emberton M: **Photodynamic therapy for focal ablation of the prostate.** *World J Urol* (2010) **28**(5):571-576.
30. Gheewala T, Skwor T, Munirathinam G: **Photosensitizers in prostate cancer therapy.** *Oncotarget* (2017) **8**(18):30524-30538.
31. Ashur I, Goldschmidt R, Pinkas I, Salomon Y, Szewczyk G, Sarna T, Scherz A: **Photocatalytic generation of oxygen radicals by the water-soluble bacteriochlorophyll derivative wst11, noncovalently bound to serum albumin.** *J Phys Chem A* (2009) **113**(28):8027-8037.
32. Brandis AS, Salomon Y, Scherz A: **Bacteriochlorophyll sensitizers in photodynamic therapy.** In: *Chlorophylls and bacteriochlorophylls: Biochemistry, biophysics, functions and applications.* Grimm B, Porra RJ, Rüdiger W, Scheer H (Eds), Springer Netherlands, Dordrecht (2006):485-494.
33. <https://wis-wander.weizmann.ac.il/life-sciences/weizmann-institute-drug-tookad%C2%AE-soluble-approved-prostate-cancer-therapy-mexico>.
34. Azzouzi A-R, Lebdaï S, Benzaghoul F, Stief C: **Vascular-targeted photodynamic therapy with tookad® soluble in localized prostate cancer: Standardization of the procedure.** *World J Urol* (2015) **33**(7):937-944.
35. • Azzouzi A-R, Vincendeau S, Barret E, Cicco A, Kleinclauss F, van der Poel HG, Stief CG, Rassweiler J, Salomon G, Solsona E, Alcaraz A *et al*: **Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (clin1001 pcm301): An open-label, phase 3, randomised controlled trial.** *Lancet Oncol* (2017) **18**(2):181-191.

36. Sainuddin T, McCain J, Pinto M, Yin H, Gibson J, Hetu M, McFarland SA: **Organometallic Ru(II) photosensitizers derived from π -expansive cyclometalating ligands: Surprising theranostic pdt effects.** *Inorg Chem* (2016) **55**(1):83-95.