Metal-based photosensitizers for photodynamic therapy: the future of multimodal oncology?
Sherri A. McFarland¹,²,⁵, Arkady Mandel³,⁶, Roger Dumoulin-White³,⁶ and Gilles Gasser⁴,⁷

Abstract
Photodynamic 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 photosensitizer (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.

Addresses
¹ The University of Texas at Arlington, Department of Chemistry and Biochemistry, Arlington, TX 76019-0065, USA
² The University of North Carolina at Greensboro, Department of Chemistry and Biochemistry, Greensboro, NC 27402-6170, USA
³ Theralase Technologies Inc., Toronto, Ontario, Canada
⁴ Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, Laboratory for Inorganic Chemical Biology, F-75005 Paris, France

Corresponding authors: Gasser, Gilles (gilles.gasser@chimieparistech.psl.eu); McFarland, Sherri A (sherri.mcfarland@uta.edu)

Current Opinion in Chemical Biology 2020, 56:23–27
This review comes from a themed issue on Next generation therapeutics
Edited by Gonçalo Bernardes and Raphael Rodriguez
For a complete overview see the Issue and the Editorial

Keywords
Bioinorganic chemistry, Medicinal inorganic chemistry, Metals in medicine, Photodynamic therapy, Photosensitizer.

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. Photodynamic therapy (PDT) has existed for over 100 years, albeit 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 photosensitizer (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 nontoxic 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 intersystem crossing (ISC) to form the reactive triplet state. The triplet state then sensitizes cytotoxic singlet oxygen (¹O₂) through type II energy transfer or participates in type I electron transfer reactions to generate other reactive oxygen species 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 ¹O₂ 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 United States, 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 (Figure 1) [10,18].

While Photofrin set the standard for PDT, there is ongoing interest in developing the next generation of PSs that address some limitations of the tetrapyrolic systems. Single-agent, aqueous-soluble PSs that are...
preparied in high purity from straightforward syntheses are highly desirable. Low photobleaching rates, high selectivity for tumors, strong PDT effects with high irradiances and favorable pharmacokinetic 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, whereas Paryltn®, 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 coworkers in Israel and is the improved watersoluble 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 noncovalent 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 1O2, TOOKAD® Soluble appears to function exclusively through type I photo reactions, generating only superoxide (O2) and hydroxyl radicals (OH) [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]. Although 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 metalated PS compared with free Bchl [32]. Importantly, metalation 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 min 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 min and 15 s. 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 reactive oxygen species 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 centers and community hospitals) that included 206 patients receiving treatment compared with 207 patients on active surveillance [35]. All patients were men with low-risk localized prostate cancer. The study concluded that TOOKAD® Soluble was a safe and effective treatment for low-risk, localized prostate cancer [35]. After 24 months, only 28% of the men in the treatment group had disease progression compared with 38% in the active surveillance group. Impressively, 49% of the treated men had a negative prostate biopsy result 24 months after VTP, whereas only 14% of the men in the active surveillance group had this same result.

TLD-1433

TLD-1433, or [Ru(4,4’-dimethyl-2,2’-bipyridine)Cl2 (4,4’-dimethyl-2,2’-bipyridine; IP = imidazo[4,5-j] [1,10]phenanthroline; 3T = a-terthienyl, Figure 1), is the first ruthenium-based PS to advance to clinical studies and is being investigated to treat nonmuscle invasive bladder cancer (NMIBC) with PDT. It is a nonmacrocyclic, nonpyrrolic 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) and intraligand charge transfer (3ILCT) triplet excited states of significant ππ* character that have prolonged excited state lifetimes. These states sensitize 1O2 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 3IL/3ILCT 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 min 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 of approximately 90 min. 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 1–1.5 h, 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 who previously failed bacillus Calmette Guérin (BCG) therapy and were not considered candidates for (or recommended starting dose (0.35 mg/cm²). The primary (safety and tolerability), secondary (pharmacokinetics), 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 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, 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 enroll and treat approximately 100–125 patients with NMIBC (approximately 20 Canadian and US sites) that present with carcinoma in situ, 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. The secondary objective is duration of CR, measured by CR 360 days after initial PDT; and the tertiary objective is of safety, measured by adverse events that are ≥ 4, that do not resolve within 360 days after initial PDT. These patients will receive two optimized PDT (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.

Conflict of interest statement
Theralase licenses the exclusive worldwide rights for TLD-1433 and its associated PDCs.

Acknowledgements
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.

References
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest


17. https://doi.org/10.24931/2413-9432-2015-4-1-3-10


