Intraoperative 5‑ALA photodynamic therapy for newly diagnosed glioblastoma patients: a preliminary analysis of the INDYGO clinical trial (NCT03048240)

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Glioblastoma (GBM) is the most aggressive malignant primary brain tumor. The unfavorable prognosis despite maximal therapy relates to high propensity for recurrence. Thus, overall survival (OS) is quite limited and local failure remains the fundamental problem.
A safety and feasibility trial after treating GBM intraoperatively by photodynamic therapy (PDT) after 5-aminolevulinic acid (5-ALA) administration and maximal resection was performed at The Lille University Hospital, France.
Ten patients with newly diagnosed GBM were enrolled and treated between May 2017 and June 2018. The standardized therapeutic approach included maximal resection (near total or gross total tumor resection (GTR)) guided by 5-ALA fluorescence-guided surgery (followed by intraoperative PDT. Postoperatively, patients underwent adjuvant therapy (Stupp protocol). Follow-up included clinical examinations and brain MR imaging was performed every 3 months until tumor progression and/or death.
There were no unacceptable or unexpected toxicities or serious adverse effects. At the time of the interim analysis, the actuarial 12-months progression-free survival (PFS) rate was 60% (median 17.1 months), and the actuarial 12-months OS rate was 80% (median 23.1 months).
PDT delivered immediately after resection as an add-on therapy of this primary brain cancer is safe and may help to decrease the recurrence risk by targeting residual tumor cells in the resection cavity.

References

1. Vermandel M, Dupont C, Lecomte F, Leroy HA, Tuleasca C, Mordon S, Hadjipanayis CG, Reyns N. Standardized intraoperative 5-ALA photodynamic therapy for newly diagnosed glioblastoma patients: a preliminary analysis of the INDYGO clinical trial. J Neurooncol. 2021 Mar 20. doi: 10.1007/s11060-021-03718-6.
2. Dupont C, Vermandel M, Leroy HA, Quidet M, Lecomte F, Delhem N, Mordon S, Reyns N. INtraoperative photoDYnamic Therapy for GliOblastomas (INDYGO): Study Protocol for a Phase I Clinical Trial. Neurosurgery. 2019 Jun 1;84(6):E414-E419. doi: 10.1093/neuros/nyy324.
3. Dupont C, Mordon S, Deleporte P, Reyns N, Vermandel M. A novel device for intraoperative photodynamic therapy dedicated to glioblastoma treatment. Future Oncol. 2017 Nov;13(27):2441-2454. doi: 10.2217/fon-2017-0261.

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Synthesis and Unique Properties of Low-Symmetry Phthalocyanines

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Being a versatile class of functional dyes, phthalocyanines possess intriguing and tunable optoelectronic, photophysical, catalytic, and self-assembly properties. These characteristics, together with their high stability, render them to be used as advanced materials,[1] efficient catalysts,[2] and promising theranostic agents[3] for various applications. The properties of these macrocyclic compounds depend largely on the metal center and the axial and/or peripheral substituents. Both the nature and position of the substituents are important that can impart their intrinsic characteristics to the parent macrocycles and control the molecular packing and alignment, which in turn can alter their physical properties. Therefore, there has been considerable interest in controlled synthesis of phthalocyanines and revealing their structure-property-activity relationships. Over the last two decades, a number of synthetic methodologies for unsymmetrical and low-symmetry phthalocyanines have been reported sporadically.[4] Unfortunately, they still have various deficiencies and limitations which preclude them to be employed generally. In this presentation, we will report our recent endeavors in exploring feasible synthetic pathways to prepare isomerically pure low-symmetry phthalocyanines. The strategies involve prior linking of the phthalonitrile units, including the use of cleavable linkers, and mixed condensation of carefully selected phthalonitriles. The spectroscopic features and self-assembly properties of selected phthalocyanines, as well as the use of these compounds in photodynamic therapy and logic devices will also be reported and discussed.

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References:

(1) (a) Urbani, M.; de la Torre, G.; Nazeeruddin, M. K.; Torres, T. *Chem. Soc. Rev.* **2019**, *48*, 2738. (b) Urbani, M.; Ragoussi, M.-E.; Nazeeruddin, M. K.; Torres, T. *Coord. Chem. Rev.* **2019**, *381*, 1.
(2) Luo, D.-P.; Huang, Y.-F.; Hong, X.-Y.; Chen, D.; Li, G.-X.; Huang, X.-B.; Gao, W.-X.; Liu, M.-C.; Zhou, Y.-B.; Wu, H.-Y. *Adv. Synth. Catal.* **2019**, *361*, 961.
(3) Lo, P.-C.; Rodríguez-Morgade, M. S.; Pandey, R. K.; Ng, D. K. P.; Torres, T.; Dumoulin, F. *Chem. Soc. Rev.* **2020**, *49*, 1041.
(4) Mack, J.; Kobayashi, N. *Chem. Rev.* **2011**, *111*, 281.

Nanobody-targeted photodynamic therapy

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Nanobodies are the smallest naturally derived antibody fragments, obtained from heavy chain antibodies that exist in Camelids[1]. Nanobodies are 15 kDa proteins that can be developed for generally any target of interest and, when targeting receptors solely or over-expressed on cancers' cell surface, they can be used for molecular imaging and/or for targeted therapies. The relatively small dimensions of nanobodies combined with high binding affinities, lead to rapid tumor accumulation, homogenous distribution, and rapid clearance of unbound fractions. We took advantage of these properties and have developed an alternative approach for targeted photodynamic therapy (PDT) by conjugating photosensitizers to nanobodies[2]. After the first studies targeting the epidermal growth factor receptor (EGFR) for head and neck cancer, we have explored this targeted PDT approach with other nanobodies targeting different tumor markers. As photosensitizer, we have employed the IRDye700DX, that is a silicon phthalocyanine derivative, currently being tested in clinical trials conjugated to the monoclonal antibody cetuximab, and already approved for clinical use in Japan. Overall, with nanobody-targeted PDT, cytotoxicity is selectively induced in cells which have high target expression level. Preclinical studies have shown selective tumor necrosis[3] and significant tumor regression after a single treatment session[4]. This presentation will summarize these studies and discuss more recent results obtained with nanobody-targeted PDT.

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References

1. Hamers-Casterman, C.; Atarhouch, T.; Muyldermans, S.; Robinson, G.; Hamers, C.; Songa, E. B.; Bendahman, N.; Hamers, R., Naturally occurring antibodies devoid of light chains. *Nature* **1993,** *363* (6428), 446-8.
2. Heukers, R.; van Bergen en Henegouwen, P. M.; Oliveira, S., Nanobody-photosensitizer conjugates for targeted photodynamic therapy. *Nanomedicine : nanotechnology, biology, and medicine* **2014,** *10* (7), 1441-51.
3. van Driel, P.; Boonstra, M. C.; Slooter, M. D.; Heukers, R.; Stammes, M. A.; Snoeks, T. J. A.; de Bruijn, H. S.; van Diest, P. J.; Vahrmeijer, A. L.; van Bergen En Henegouwen, P. M. P.; van de Velde, C. J. H.; Lowik, C.; Robinson, D. J.; Oliveira, S., EGFR targeted nanobody-photosensitizer conjugates for photodynamic therapy in a pre-clinical model of head and neck cancer. *Journal of controlled release : official journal of the Controlled Release Society* **2016,** *229*, 93-105.
4. Deken, M. M.; Kijanka, M. M.; Beltran Hernandez, I.; Slooter, M. D.; de Bruijn, H. S.; van Diest, P. J.; van Bergen En Henegouwen, P. M. P.; Lowik, C.; Robinson, D. J.; Vahrmeijer, A. L.; Oliveira, S., Nanobody-targeted photodynamic therapy induces significant tumor regression of trastuzumab-resistant HER2-positive breast cancer, after a single treatment session. *Journal of controlled release : official journal of the Controlled Release Society* **2020,** *323*, 269-281.

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Plenary-4

Developing Next Generation of Molecular Scaffolds for Treatment of Challenging Cancers: An Overview

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Cancer is the second leading cause of death worldwide, accounting for a total of almost 9 million deaths in 2015. Research efforts have resulted in significant increase in 5-year survival rates for a good portion of cancer types, however, unfortunately, this is not the case for some challenging cancers such as brain cancer glioblastoma. Three fundamental issues are at the core of this reality: 1) High percentage of inoperable brain tumors; 2) Limited number of drugs that can pass through the blood-brain barrier and 3) Absence of effective targeted brain cancer therapies. Photodynamic therapy (PDT) has the potential to be a selective, effective and non-invasive alternative to current treatments, however to date it is only applicable to a small group of cancers. Realization of non-toxic, water-soluble and photostable PDT agents, with strong near infrared absorption for deep tissue penetration, that also realizes high singlet oxygen generation efficiency and effective targeting, is the key for widespread use of PDT for majority of cancers. For brain cancer specifically, low molecular weights and controlled lipophilicity is needed as well. In this talk I will try communicate our efforts for developing next generation of molecular scaffolds that have the potential to fulfill the aforementioned requirements. Specifically, our recent work on targeted resorufin agents[1] and the first example of theranostic sila-fluorescein based agents will be highlighted.[2] Additionally, our work on mitochondria targeting selenophene-BODIPY agents that shows remarkable results under hypoxia will be discussed.[3]

References

1. O. Karaman, T. Almammadov, M. E. Gedik, G. Gunaydin, S. Kolemen*, **G. Gunbas***, Mitochondria Targeting Selenophene Modified BODIPY-Based Photosensitizers for the Treatment of Hypoxic Cancer Cells, *ChemMedChem*, **2019**, *14*, 1879-18860 (Cover)

2. T. Almammadov, G. Atakan, O. Leylek, G. Ozcan, **G. Gunbas***, S. Kolemen*, Resorufin Enters the Photodynamic Therapy Arena: A Monoamine Oxidase Activatable Agent for Selective Cytotoxicity, *ACS. Med. Chem. Lett.* **2020**, *11*, 2491-2496 (Cover)

3. S. Cetin, Z. Elmazoglu, O. Karaman, H. Gunduz, **G. Gunbas***, S. Kolemen*, Balanced Intersystem Crossing in Iodinated Silicon-Fluoresceins Allows New Class of Red Shifted Theranostic Agents, *ACS. Med. Chem. Lett.* **2021** Accepted.

Pancreatic and biliary cancer: clinical studies

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Patients with non-resectable pancreatic and biliary tract cancer (cholangiocarcinoma and gallbladder cancer) have a dismal outlook with conventional therapies, with a median survival of 3-9 months and a 5 year survival of less than 3%. Surgery is the only curative treatment but is appropriate in less than 20% of cases, and even then is associated with a 5-year survival of less than 30% in selected series. Although most applications of PDT in gastroenterology have been on lesions of the luminal gut, there is increasing experimental and clinical evidence for its efficacy in cancers of the pancreas and biliary tract. In patients with unresectable cholangiocarcinoma, patients treated with stenting plus PDT have been reported to show an improvement in cholestasis, quality of life and survival compared with historical controls treated with stenting alone, although data from randomised controlled trials are conflicting and the largest study (by our group) reported a survival detriment with PDT[1]. Similarly, pancreatic adenocarcinoma often presents with unresectable locally advanced disease, for which local debulking using interstitial[2] or endoscopic ultrasound-guided[3] PDT are novel approaches. Preclinical studies of PDT in animal models have demonstrated effective tissue and tumour necrosis. Early clinical studies also suggest that PDT may be able to reduce the bulk of locally advanced pancreatic cancers using this minimally invasive technique. Further controlled studies are required to assess the true influence of PDT on survival and quality of life of patients with these cancers.

Pereira SP, Jitlal M, Duggan M, Lawrie E, Beare S, O'Donoghue P, Wasan HS, Valle JW, Bridgewater J. PHOTOSTENT-02: porfimer sodium photodynamic therapy plus stenting versus stenting alone in patients with locally advanced or metastatic biliary tract cancer. *ESMO Open* 2018; **3**: e000379.

Huggett MT, Jermyn M, Gillams A, Illing R, Mosse S, Novelli M, Kent E, Bown SG, Hasan T, Pogue BW, **Pereira SP**. Phase I/II study of verteporfin photodynamic therapy in locally advanced pancreatic cancer. *Br J Ca* 2014; **110**: 1911-21.

Hanada Y, **Pereira SP**, Pogue B, Maytin EV, Hasan T, Linn B, Mangels-Dick T, Wang KK. EUS-guided verteporfin photodynamic therapy for pancreatic cancer. *Gastrointest Endosc* 2021 Feb 26:S0016-5107(21)00177-2. Online ahead of print.

Developing new protocols for antimicrobial PDT

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Antimicrobial Photodynamic Therapy (aPDT) has been presenting as an efficient and safe alternative for the treatment of localized infections as of infected ulcers, periodontal disease, onychomycosis, among others[1]. Especially when considering the alarming context of the consequences of antimicrobial resistance where it is predicted over 10 million global deaths per year by 2050, if no effective measurements are taken[2], aPDT may be considered as a potential treatment option. Due to its mechanism of action, mainly based on the production of the highly reactive singlet oxygen, aPDT presents a response that is non-biological site specific resulting in the potential inactivation of bacteria, fungi, and virus. The development of new aPDT protocols are based on *in vitro* experiments to determine the best photosensitizer type for the target microorganism and proof-of-concept of the inactivation response, validation of antimicrobial response and safety at animal model and preclinical and clinical trials. Examples of the aPDT protocols and instrumentation developed for pythiosis[3,4] and decontamination of lungs for transplantion[5] will be discussed.

References

(1) Kharkwal, G. B.; Sharma, S. K.; Huang, Y. Y.; Dai, T.; Hamblin, M. R. Photodynamic Therapy for Infections: Clinical Applications. *Lasers in Surgery and Medicine*. 2011. https://doi.org/10.1002/lsm.21080.
(2) IAGG. *No Time to Wait*; 2019.
(3) Pires, L.; Bosco, S. D. M. G.; Baptista, M. S.; Kurachi, C. Photodynamic Therapy in Pythium Insidiosum - An in Vitro Study of the Correlation of Sensitizer Localization and Cell Death. *PLoS One* **2014**, *9* (1), 1–8. https://doi.org/10.1371/journal.pone.0085431.
(4) Pires, L.; Bosco, S. de M. G.; da Silva Junior, N. F.; Kurachi, C. Photodynamic Therapy for Pythiosis. *Vet. Dermatol.* **2013**, *24* (1), 130–137. https://doi.org/10.1111/j.1365-3164.2012.01112.x.
(5) Galasso, M.; Feld, J. J.; Watanabe, Y.; Pipkin, M.; Summers, C.; Ali, A.; Qaqish, R.; Chen, M.; Ribeiro, R. V. P.; Ramadan, K.; Pires, L.; Bagnato, V. S.; Kurachi, C.; Cherepanov, V.; Moonen, G.; Gazzalle, A.; Waddell, T. K.; Liu, M.; Keshavjee, S.; Wilson, B. C.; Humar, A.; Cypel, M. Inactivating Hepatitis C Virus in Donor Lungs Using Light Therapies during Normothermic Ex Vivo Lung Perfusion. *Nat. Commun.* **2019**, *10* (1), 481. https://doi.org/10.1038/s41467-018-08261-z.

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Plenary-7

The many faces of Photodynamic Activation: a tool for effective nanomedicine?

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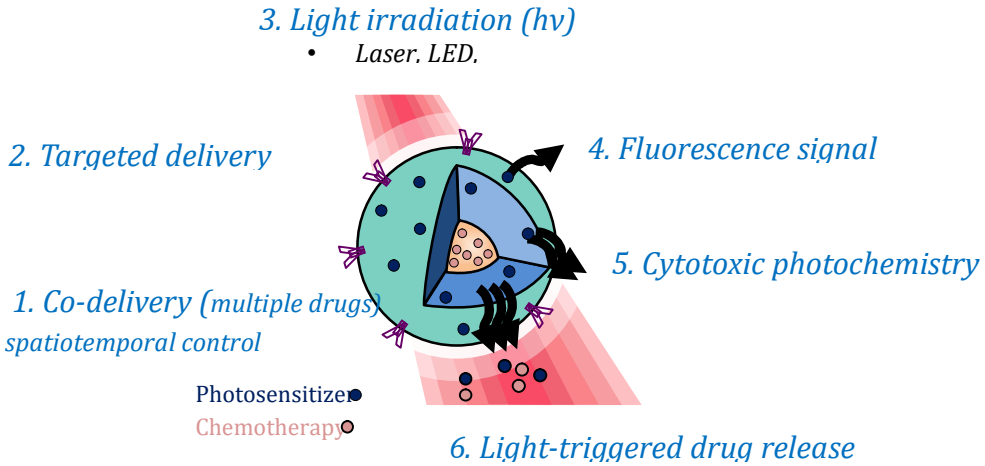
Light activation of materials leads to thermal, photochemical and radiative processes which can be captured for response-based therapeutic design. Photodynamic therapy (PDT) captures the photochemical processes that ensue such an activation. The ability to use light as a reagent to control drug release further allows for the fabrication of light controllable intelligent multiagent constructs that attack multiple pathways making the nanomedicines more effective against cancer. In the case of cancer, combination therapy is now a routine standard of care for most cancers and situations. It is also used for the management of other diseases. Typically, these are administered separately with their own pharmacokinetics, hitting targets at different times which reduces the synergism potential. Nanomedicines, overcomes the temporal limitation by delivering the multiple agents to the target site at the same time. And, provided there is synergism between the agents, the interaction will be maximized as the drugs or toxic species will act at the same time at the same place. In PDT the requirement of light and the photosensitizer being present at the same place at the same time there is an additional level of selectivity. Neither light alone nor the photosensitizer have an effect on target cells by themselves. In addition to the direct cytotoxic effect, the photodynamic activation primes the microenvironment in a process call *P*hoto*D*ynamic *P*riming (PDP) to enable a more potent response to conventional treatments, so the PDP becomes an enabler of other treatments, particularly when administered in a Nanoplatform. Strategies for syntheses and applications in biology and medicine will be discussed. The essentials of the platform are presented in the conceptual Figure 1 below.



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COP-1

Tetra vs Octa - How it affects the physicochemical, photophysical, photochemical and biological properties of mercaptophenol-substituted phthalocyanines

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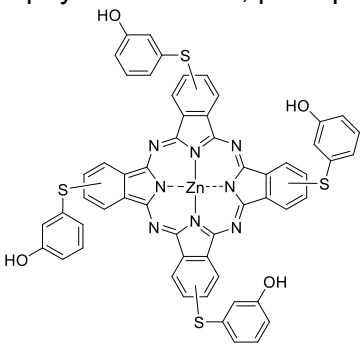
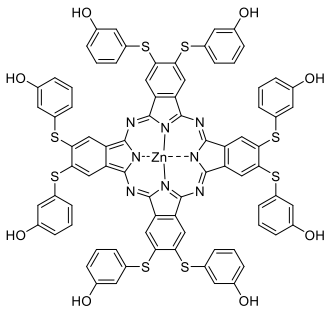
The introduction of a sulfur donor grafting atom on the periphery of the Pcs confers excellent spectroscopic and photochemical properties, which are known to be very sensitive to the substitution pattern[1].

In this study, symmetrically tetra and octa zinc phthalocyanines peripherally substituted with 3-mercaptophenol groups were synthesized and characterized by FT-IR, UV-Vis, NMR spectroscopy and mass spectra.

The effect of the tetra vs octa substitution pattern has been investigated from the point of view of their physicochemical, photophysical, photochemical and biological properties.





1. Modulation of the electronic and spectroscopic properties of Zn(II) phthalocyanines by their substitution pattern
Sevinc Z. Topal, Ümit İşci, Ufuk Kumru, Devrim Atilla, Ayşe G. Gürek, Catherine Hirel, Mahmut Durmuş, Jean-Bernard Tommasino, Dominique Luneau, Savas Berber, Fabienne Dumoulin* and Vefa Ahsen*, *Dalton Trans.* **2014**, *43*, 6897-6908

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COP-2

Development of Advanced Photodynamic Molecular Beacons with Multiple Controls for Targeted Photodynamic Therapy

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Photodynamic therapy (PDT) is an established treatment modality for various superficial and localized cancers.[1] It utilizes the combined action of a photosensitizer, light of appropriate wavelength, and oxygen to generate reactive oxygen species (ROS) to eradicate cancer cells. Owing to the very short lifetime (< 40 ns) and diffusion range (ca. 20 nm) of ROS, their action is almost confined to the site where ROS are produced. Therefore, preferential localization of the photosensitizer in tumor and precise application of the light are extremely crucial that can greatly improve the therapeutic outcome. Considerable efforts have therefore been put to enhance the tumor-targeting property and pharmacokinetic profiles of photosensitizers, and to advance the fiber optics and endoscopy technologies. Apart from directing the photosensitizers to the tumor through conjugation with tumor-targeting ligands or encapsulation into multifunctional nanocarriers, controlling their photoactivity in a specific manner is another promising approach. These so-called photodynamic molecular beacons (PMBs) are either self-quenched or deactivated by the quenching component in the native form, but upon interactions with cancer-related stimuli, the photosensitizing units are activated through disaggregation or separation from the quenchers, resulting in restoration of their fluorescence and ROS generation. This approach can minimize the photodamage of normal tissues in PDT. To further improve the tumor specificity and therapeutic efficacy, it is desirable that the PMBs can only be activated by the coexistence of more than one stimulus or conjugate to a tumor-targeting ligand. In this presentation, we will report two dual activatable zinc(II) phthalocyanine (ZnPc)-based PMBs, which are fully activated in the presence of both glutathione and cathepsin B.[2] The chemical synthesis, characterization, stimuli-responsive photophysical properties, and in vitro photodyamic activities of these PMBs will be presented.

References:

1. van Straten, D.; Mashayekhi, V.; de Bruijn, H. S.; Oliveira, S.; Robinson, D. J. Oncological Photodynamic Therapy: Basic Principles, Current Clinical Status and Future Directions. *Cancers* **2017**, *9*, 19.

2. Tam, L. K. B.; Yu, L.; Ng, D. K. P.; P.-C. Lo, Unpublished results.

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COP-3

The photodynamic efficacy of asymmetric heteroleptic A_7B type novel lanthanide bis-phthalocyanine complexes

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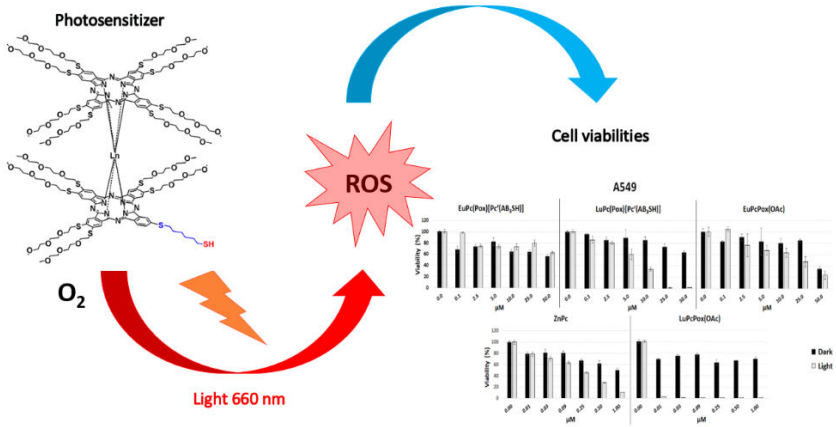
Among the new generation Pc complexes, lanthanide(III) phthalocyanines are of a high interest because of possible coordination of two or more Pc macrocyclic units per metal atom forming $LnPc_2$, or Ln_2Pc_3[1-2] These lanthanide bisphthalocyanine derivatives exhibit high intrinsic electrical conductivity with exciting electrochemical and electrochromic properties[3]. The optical properties of $LnPc_2$ such as higher extinction coefficient in the far-red region (>670 nm) with an optimal singlet oxygen quantum yield (>0.3) and red-shifted fuorescence (>680 nm) are favorable for PDT applications. In this study we focused on the A_7B target asymmetric heteroleptic bisPcs with a polar thiol group for the "B" part, and for A part hydrophobic polyoxyethylene chains in the PDT application as photosensitizers. They can be activated with specifc light irradiation and produce reactive oxygen species (ROS) such as singlet oxygen, oxygen free radicals that may be produced only in the irradiated area. Therefore, it is crucial to evaluate toxic infuence of PSs by measuring cell viability and to determine IC50 values *in vitro* conditions. We demonstrated that LuPcPox(OAc) among the Pcs tested offers higher photodynamic efficacy for A549 and BEAS-2B cells *in vitro* conditions[4].



. Thomas, A. L., *Phthalocyanine Research and Applications*, Taylor & Francis, 1990
2. Kalashnikova, I., Nefedov, S., Tomilova, L. and Zefirov, N., *Russ. Chem. Bull., 2007, 56, 2426–2432*
3. Bian, Y., Zhang, Y., Ou, Z. and Jiang, J., *Handbook of Porphyrin Science: With Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine*, 2011
4. Önal, E., Tüncel, Ö., Albakour, M., Gümüşgöz Çelik, G., Gürek, A.G., Özçelik, S., *RSC Advances., 2021, 11, 6188*

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COP-4

Computational investigation of chemical and photophysical properties of two-component Pt(II)-BODIPY dyes

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Photodynamic Therapy (PDT) is a worldwide accepted, minimally invasive and non-toxic light assisted treatment of different cancer cell types and other non-malignant diseases. PDT is based on the generation of reactive oxygen species (ROS). PDT involves three components, namely a nontoxic photosensitizer (PS), light of a specific wavelength (usually in the visible spectrum)and molecular oxygen.

The therapy relies on the ability of the PS, a molecule with specific chemical and photophysical properties, to trigger, upon activation, a series of photochemical and photobiological reactions that induce apoptosis and/or necrosis in the tumor cells through the production of intracellular reactive oxygen species (ROS), singlet oxygen $^1O_2$ and free radicals.

Owing to the success of the boron dipyrromethane (BODIPY) dye in PDT practice and of cisplatin in chemotherapy, particular attention is paid to two-component PtII-BODIPY systems, a new class of compounds with a dual-target effect. Moreover, experimental studies have shown how the introduction of platinum in the BODIPY skeleton can improve, upon irradiation and at low concentration, the phototoxicity of BODIPY, ¸also increasing the cellular accumulation.[1,2]

In this work, with the aim of revealing the influence of the platinum complex on the physicochemical behavior of the PSs, the photophysical and chemical properties of two new synthesized BODIPYs and their conjugates with cisplatin moiety have been theoretically explored. In addition, the mechanism of the hydrolysis reaction of the platinum complexes, conjugated with the BODIPY, has been investigated.

References

1 Liu, Y.; Li, Z.; Chen, L. and Xie, Z. Near infrared BODIPY-Platinum conjugates for imaging, photodynamic therapy and chemotherapy, *Dyes and Pigments,* **2017**, *141*, 5–12.

2 Xue, X.; Zhu, C.; Chen, H.; Bai, Y.; Shi, X.; Jiao, Y.; Chen, Z.; Miao, Y.; He, W. and Guo, Z. A New Approach to Sensitize Antitumor Monofunctional Platinum(II) Complexes via Short Time Photo-Irradiation. *Inorg Chem,* **2017**, *56* (7), 3754–3762.

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COP-5

Periodic Mesoporous Ionosilica Nanoparticles for Green Light Photodynamic Therapy and Photochemical Internalization of siRNA

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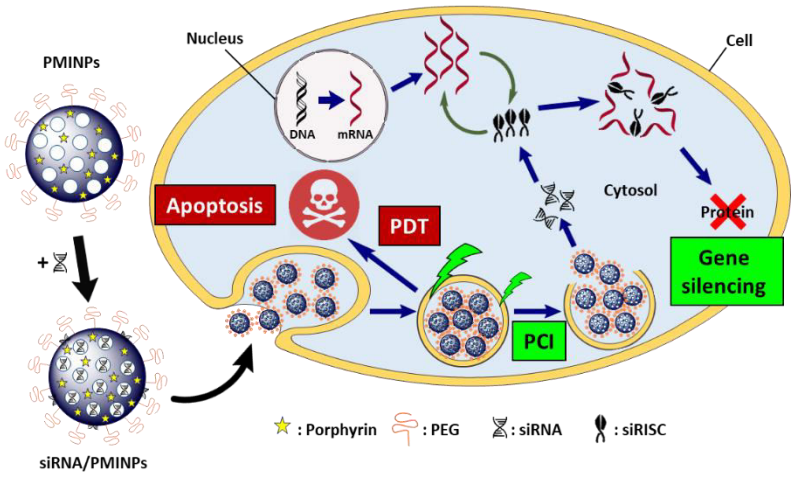
ABSTRACT



We report the use of Periodic Mesoporous Ionosilica Nanoparticles (PMINPs) as versatile nano-objects for imaging, photodynamic therapy (PDT), and efficient adsorption and delivery of siRNA into breast cancer cells. Mesoporous ionosilica nanoparticles display several interesting features: high specific area and uniformity of both size and shape of pores, together with a very particular interfacial properties, induced by the high density of immobilized ionic groups. In order to confer to these nanoparticles PDT and siRNA photochemical internalization (PCI) properties, a porphyrin derivative was integrated into the ionosilica framework.

For this purpose, we synthetized PMINPs via hydrolysis - polycondensation procedures, starting from oligosilylated ammonium and porphyrin precursors. The formation of these nano-objects was attested by TEM. The formed nanoparticles were then thoroughly characterized via solid state NMR, nitrogen sorption and DLS. The spectral properties of these nanoparticles were also studied using UV-Vis and fluorescence spectroscopy, attesting the successful incorporation of the porphyrin derivative within the ionosilica matrix.
Our results indicate the formation of highly porous nanorods (1015 $m^2 g^{-1}$) with 108 ± 9 nm in length and 54 ± 4 nm in width. A significant PDT effect of type (I) mechanism (95 ± 2.8% of cell death) was observed, due to an important ROS production upon green light irradiation (15 min at 545 nm, 34 J cm^{-2}) in nanoparticles treated-breast cancer cells. Zeta potential measurements of PMINPs revealed the presence of positive surface charges (+35.8 mV), which promoted the complexation of siRNA. The electrostatic complexation of siRNA was then verified by electrophoresis gel retardation assay. PMINPs formed stable complexes with siRNA (up to 24 hours) and were efficiently internalized into the cells after 4 hours incubation mostly with energy-dependent endocytosis process. The PCI effect was obvious under green light irradiation (5 min at 545 nm, 11.3 J cm^{-2}) and successfully led to 83 ± 1.1% silencing of luciferase gene in luciferase expressing breast cancer cells, while no gene silencing effect was observed in the absence of light.
This work highlights the high potential of porphyrin-doped PMINPs as multifunctional nanocarriers for nucleic acids, such as siRNA, with a triple ability to perform imaging, PDT and PCI.

KEYWORDS

Mesoporous ionosilica nanoparticles, siRNA, PDT, PCI, gene silencing, cancer.

REFERENCE

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COP-6

Photocatalytic Activation And Delivery Of Pt Anticancer Drugs

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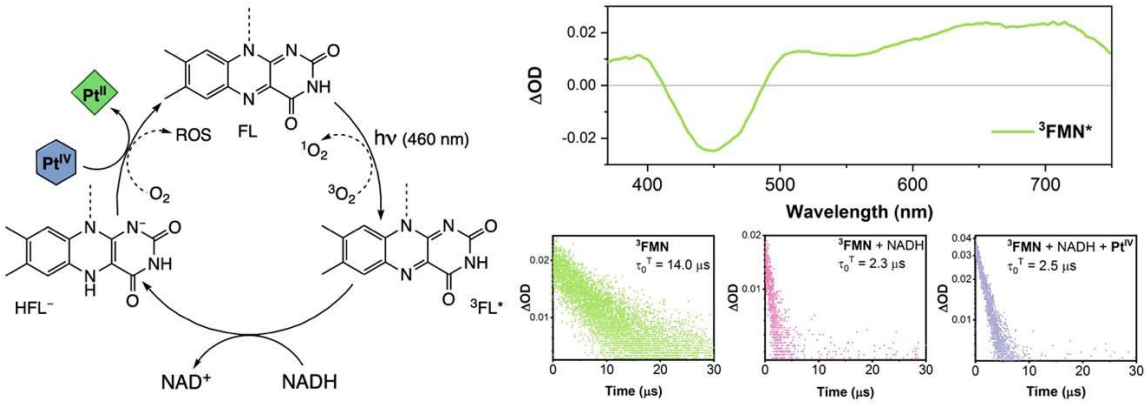
In catalysis, coordination and organometallic compounds typically operate as catalysts for the transformation of organic compounds into added value chemicals. Conversely, catalytic reactions in which metal complexes act as substrates are practically unknown.
My group recently discovered that flavins photocatalyze the conversion of Pt(IV) precursors into Pt(II) anticancer drugs in the presence of electron donors.[1-3] These reactions have bioorthogonal selectivity, occurring in biological environments with high efficiency.
In this contribution, I will describe how this unconventional chemistry can be exploited to devise innovative strategies for photochemotherapy,[4] including by designing flavin-based biomaterials for drug photodelivery.[5]



References
1. Alonso-de Castro, S.; Ruggiero, E.; Ruiz-de-Angulo, A.; Rezabal, E.; Mareque-Rivas, J. C.; Lopez, X.; López-Gallego, F.; Salassa, L. *Chem. Sci.* **2017**, *8*, 4619–4625.
2. Alonso-de Castro, S.; Cortajarena, A. L.; López-Gallego, F.; Salassa, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 3143–3147.
3. Gurruchaga-Pereda, J.; Martínez-Martínez, V.; Rezabal, E.; Lopez, X.; Garino, C.; Mancin, F.; Cortajarena, A. L.; Salassa, L. *ACS Catal.* **2020**, *10*, 187–196.
4. Alonso-de Castro, S.; Terenzi, A.; Hager, S.; Englinger, B.; Faraone, A.; Calvo Martínez, J.; Galanski, M.; Keppler, B. K.; Berger, W.; Salassa, L. *Sci. Rep.* **2018**, *8*, 17198.
5. Mazzei, L.F.; Martínez, A.; Trevisan, L.; Rosa-Gastaldo, D.; Cortajarena, A. L.; Mancin, F.; Salassa, L. *Chem. Commun.* **2020**, *56*, 10461-10464.

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COP-7

Evaluation of Histone Deacetylase Inhibitor Substituted Zinc and Indium Phthalocyanines for Chemo- and Photodynamic Therapy

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Due to its specificity and selectivity, Photodynamic Therapy (PDT) has gained extensive attention and became a treatment option for various medical conditions[1]. Phthalocyanines (Pcs), stable synthetic macromolecules that absorb light at a long-wavelength and generate high levels of reactive oxygen species (ROS) are frequently used in anti-cancer PDT applications[2]. Substitution of various chemotherapeutics with Pcs is a novel approach that alleviates compounds' hydrophobicity while increasing their efficacy[3]. Histone deacetylases (HDACs) regulate post-translational protein modifications and are directly involved in cancer pathogenesis[4]. Herein, we designed novel zinc (Zn) and indium (In) Pc derivatives, substituted with a histone deacetylase inhibitor (HDACi), 3-hydroxypyridin-2-thione (3-HPT) either non-peripherally or peripherally that combines photodynamic activity of Pcs and chemotherapeutic action of 3-HPT, and evaluated the anti-cancer properties of the compounds on two different breast cancer cell lines (non-invasive MCF-7 and invasive MDA-MB-231 cells) as well as on a healthy human endothelial cell line (HUVEC).
All compounds induced cell death, cell cycle arrest and mitochondrial ROS accumulation, downregulated HDAC6 along with either CD44 or CCR7 protein levels, or both, suggesting that PDT along with HDAC inhibition may be beneficial for breast cancer treatment.

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References:

1. Rak, J.; Pouckova, P.; Benes, J.; Vetvicka, D. Drug Delivery Systems for Phthalocyanines for Photodynamic Therapy. *Anticancer Res.* **2019**, 39, 3323– 3339, DOI: 10.21873/anticanres.13475
2. Lo, P.-C.; Rodríguez-Morgade, M. S.; Pandey, R. K.; Ng, D. K. P.; Torres, T.; Dumoulin, F. The unique features and promises of phthalocyanines as advanced photosensitisers for photodynamic therapy of cancer. *Chem. Soc. Rev*. **2020**, 49, 1041– 1056, DOI: 10.1039/C9CS00129H2.
3. Lazaro-Carrillo, A.; Simões, B. M.; Clarke, R. B.; Villanueva, A. PO-010 Dual chemotherapy and photodynamic therapy: a synergistic strategy to improve cancer treatment. *ESMO Open* **2018**, 3, A231.1– A231, DOI: 10.1136/esmoopen-2018-EACR25.545
4. Minucci, S.; Pelicci, P. G. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. *Nat. Rev. Cancer* **2006**, 6, 38– 51, DOI: 10.1038/nrc1779.

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COP-8

Synthesis and photophysical studies of porphyrin-lignin conjugates

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Porphyrins are the most studied and well-known photosensitizers (PSs) used in photodynamic therapy (PDT).[1] Upon light irradiation, porphyrin PSs are capable of generating singlet oxygen and reactive oxygen species, and possess tumour localizing properties.[2] Combining the production of these reactive oxygen species and their biological uptake, these compounds seemed to be ideal PSs.

However over the last two decades, porphyrins by themselves, or so-called "first generation PSs", have shown to possess several disadvantages that include mainly poor near infrared light absorption and cutaneous photosentivity.[3] In the last 15 years, research into the so called "second generation" and "third generation" PSs has led to a plethora of porphyrin derivatives being synthesized with the aim of improving its photodynamic efficacy against cancer.[4] The PEIRENE laboratory in Limoges, France, has a large variety of interdiscplinary experience in the investigation of porphyrins (and their derivatives) for photodynamic therapy. Furthermore, they have experience in the chemical modification of lignin to further investigate it's potential. Lignin, a side-product made in the paper industry, has been used in delivery systems for different pharmaceutical applications and more recently has been reported to produce singlet oxygen once acetylated.[5, 6] Within this work, and with the aim of improving the photodynamic efficacy of porphyrinoid species, novel porphyrin-lignin conjugates were synthesized that display improved photophyiscal properties compared to their porphyrin parent compounds.

References:

1. Pushpan, S. K.; Venkatraman, S.; Anand, V. G.; Sankar, J.; Parmeswaran, D.; Ganesan, S.; Chandrashekar, T. K. Porphyrins in Photodynamic Therapy - a Search for Ideal Photosensitizers. *Current Medicinal Chemistry – Anti-Cancer Agents*. **2002**, *2* (2), 187–207.
2. Dąbrowski, J. M.; Pucelik, B.; Regiel-Futyra, A.; Brindell, M.; Mazuryk, O.; Kyzioł, A.; Stochel, G.; Macyk, W.; Arnaut, L. G. Engineering of relevant photodynamic processes through structural modifications of metallotetrapyrrolic photosensitizers. *Coord. Chem. Rev.* **2016**, *325* (1), 67–101.
3. O'Connor, A. E.; Gallagher, W. M.; Byrne, A. T. Porphyrin and Nonporphyrin Photosensitizers in Oncology: Preclinical and Clinical Advances in Photodynamic Therapy. *Photochem. Photobiol.* **2009**, *85* (5), 1053–1074.

4. Gomes, A. T. P. C.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. Cancer, Photodynamic Therapy and Porphyrin-Type Derivatives. *An. Acad. Bras. Cienc.* **2018**, *90* (1), 993–1026.
5. Figueiredo, P.; Lintinen, K.; Hirvonen, J. T.; Kostiainen, M. A.; Santos, H. A. Properties and Chemical Modifications of Lignin: Towards Lignin-Based Nanomaterials for Biomedical Applications. *Prog. Mater. Sci.* **2018**, *93* (1), 233–269.
6. Marchand, G.; Calliste, C. A.; Williams, R. M.; McLure, C.; Leroy-Lhez, S.; Villandier, N. Acetylated Lignins: A Potential Bio-Sourced Photosensitizer. *ChemistrySelect.* **2018,** *20* (3), 5512–5516.

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Investigation of metallo-surfactant based nanocolloids for photodynamic therapy

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Metallosurfactant (MS) aggregates have grasped great attention from researchers worldwide due to the dual properties of both metals and surfactants. On complexing surfactants with metal ions, depression in the critical micelle concentration (CMC) is usually observed compared to those of the parent surfactants[1,2]. Catanionic vesicles are synthesized by mixing cationic and anionic surfactant into a non-stoichiometric ratio which leads to spontaneous vesicle formations. These vesicles can control the size, surface charge by varying the cationic/anionic ratio. Photodynamic therapy is a combination of photosensitive drugs, the light of specific wavelengths, and molecular oxygen. Light of suitable wavelength hit the photosensitizer (PS) which then converts molecular oxygen into singlet oxygen in PS triplet excited state[3,4]. We have prepared metallocatanionic vesicles from a combination of a double-and single-chain copper and Iron-based cationic metallosurfactant (CuCPCII, CuCPCI, and FeCPCII, FeCPCI) and an anionic surfactant sodium bis(2-ethylhexyl)sulfosuccinate (AOT). We have prepared a different ratio from 10:90 to 90:10 in PBS of 7.4 pH. In this approach, two of the fractions, one each from a cationic rich and anionic rich side, were selected to encapsulate anionic (rose bengal (RB)) PSs. It was characterized by SAXS, AFM, FE-SEM, Zeta-sizer, and conductivity measurements. These studies reveal that the MCV has dual functionality *i.e.* encapsulate PSs and even show antibacterial properties against *S. Aureus, E. Coli.* MCV *help in enhancing the singlet oxygen yield of RB.* We have applied these PS loaded MCV against U-251 Glioblastoma cell lines. This experiment shown high phototoxicity against cancer cell lines which were confirmed by WST-8 assay. This work provides a new metal hybrid smart material that possesses dual functionality and is prepared by an easy, economical, and feasible procedure which resulted in enhanced PDT against a drug-resistant bacterium and cancer cell lines.

References-

1. Kaur, G.; Kumar, S.; Dilbaghi, N.; Bhanjana, G.; Guru,K. S.; Bhushan, S.; Jaglan, S.; Hassan, P. A.; Aswal, V. K. Hybrid surfactants decorated with copper ions: aggregation behavior, antimicrobial activity and antiproliferative effect, *Phys. Chem. Chem. Phys.*, **2016,** 18, 23961-23971.

2. Kaur, N.; Kaur, S.; Kaur, G.; Bhalla, A.; Srinivasan, S.; Chaudhary, G. R. Metallovesicles as smart nanoreactors for green catalytic synthesis of benzimidazole derivatives in water, *J. Mater. Chem. A*, **2019**, 7, 17306-17314.

3. Sharma, B.; Kaur, G.; Chaudhary, G. R.; Gawali, S. L.; Hassan, P. A. High antimicrobial photodynamic activity of photosensitizer encapsulated dual-functional metallocatanionic vesicles against drugresistant bacteria S aureus. *Biomater. Sci*. **2020**, 8, 2905−2920.

4. Sharma, B.; Kaur, G.; Chaudhary, G. R. Optimization and utilization of single chain metallocatanionic vesicles for antibacterial photodynamic therapy (aPDT) against E. Coli, *J. Mater. Chem. B*, **2020,** 8, 9304-9313.

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COP-10

Cetuximab-Ag_2S Quantum Dots for Fluorescent Imaging and Highly Effective Combination of ALA-based Photodynamic/Chemo-therapy of Colorectal Cancer Cells

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Colorectal Cancer (CRC) show poor prognosis with drug-resistance, severe off-site drug-toxicity and a low survival rate [1]. 5-Aminolevulinic acid (ALA) based photodynamic therapy (PDT) is very popular in recent years to treat several cancers but not yet well investigated for CRC ALA is converted to photosensitiser, protoprophyrin (PpIX), most effectively by the cancerous cells and cause phototoxicity when irradiated with a non-ionising light, providing some specificity and locality to the treatment [2], [3]. But ALA-PDT requires enhanced accumulation of ALA at the tumour site as well. Herein, theranostic nanoparticles offering tumour specificity, enhanced PDT or PDT-chemotherapy combination and optical imaging in the near-infrared (NIR) are described for EGFR(+) CRC cells [4], [5]. These are composed of Ag_2S quantum dots (AS-2MPA) conjugated with Cetuximab (Cet) and loaded with ALA or ALA/5-fluorouracil (5FU) SW480, HCT116, and HT29 cells with decreasing EGFR expression level were studied. Cet-conjugated QDs endowed excellent targeting of the high EGFR expressing cells and showed a strong intracellular signal for optical detection. The efficiency of the cells in

PpIX production decreased in the order of SW480-HT29-HCT116; hence therapeutic efficacy of the theranostic QDs were evaluated in 2D cell cultures and 3D spheroids of SW480 and HT29. PDT was performed at 420 nm (blue lamp-5 min) and 640 nm (diode laser-1 min) using QDs with either electrostatically loaded, hydrazone or amide linked ALA to achieve a different level of pH-sensitive release. AS-2MPA-ALA-electrostatic always performed better than free ALA due to improved uptake and the other ALA conjugated QDs with fastest ALA release in acidic pH. SW480 cells were more sensitive to PDT and reduced IC50 below 0.347 mM [ALA] even after 4 h incubation. In 2D and 3D cell cultures, AS-2MPA-ALA-electrostatic-Cet+420 nm irradiation reduced the viability below 30% in SW480 and 40% in HT29 which was further reduced below 18% and 30%, respectively, with codelivery of ALA/5FU. Long incubation time and 640 irradiations both cells (2D) caused dramatic toxicity reaching near-complete elimination of viable cells at 0.347 mM [ALA]/15 µg/mL [5FU]. Toxicity was correlated with high levels of reactive-oxygen species (ROS) and apoptotic/necrotic cell death. Hence, both AS-2MPA-ALA-Cet based PDT and AS-2MPA-ALA-Cet-5FU based Chemo/PDT combination therapy coupled with strong NIR tracking of the QDs demonstrate an exceptional therapeutic effect on CRC cells and an excellent potential for synergistic multistage tumour targeting therapy.

Reference:

[1] Y. Shih *et al.*, “EGFR-targeted micelles containing near-infrared dye for enhanced photothermal therapy in colorectal cancer,” *J. Control. Release*, vol. 258, no. August 2016, pp. 196–207, 2017.

[2] H. Xu *et al.*, “Effects of light irradiation upon photodynamic therapy based on 5-aminolevulinic acid–gold nanoparticle conjugates in K562 cells via singlet oxygen generation,” *Int. J. Nanomedicine*, p. 5029, 2012.

[3] J. Chen *et al.*, “Nanomaterials as photothermal therapeutic agents,” *Prog. Mater. Sci.*, vol. 99, no. May 2017, pp. 1–26, 2019.

[4] M. Hashemkhani, K. Bilici, and A. Muti, “Ag 2 S-Glutathione quantum dots for NIR image guided photothermal therapy” 2020.

[5] F. Wen and Q. Li, “2016 Colorectal Cancer : Global view Treatment dilemmas of cetuximab combined with chemotherapy for metastatic colorectal cancer,” vol. 22, no. 23, pp. 5332–5341, 2016.

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COP-11

Photodynamic Therapy using a New Folate Receptor-Targeted Photosensitizer on Peritoneal Ovarian Cancer Cells Induces the Release of Extra-cellular Vesicles with Immunoactivating Properties

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Background: Often discovered at an advanced stage, ovarian cancer progresses to peritoneal carcinoma, which corresponds to the invasion of the serosa by multiple tumor implants. The current treatment is based on the combination of chemotherapy and tumor cytoreduction surgery. Despite the progress and standardization of surgical techniques combined with effective chemotherapy, the occurrence of recurrences keeps and affects more than 60% of women in remission at the end of this treatment. Photodynamic therapy (PDT) is particularly indicated for the treatment of superficial lesions on a large surface and appears to be a relevant candidate for the treatment of microscopic intraperitoneal lesions and for non-visible lesions. However, the impact of this therapy on immune cells remains unclear.

Approach and Results: Hence, the objective of this study was to validate the efficacy of a new photosensitizer [pyropheophorbide a-polyethylene glycol-folic acid (PS^{AF})] on human ovarian cancer cells and to assess the impact of the secretome of PDT-treated cells on human peripheral blood mononuclear cells (PBMC). We showed that PS^{AF} upon illumination could induce *in vitro* cell death of different ovarian tumor cells and *in vivo* a limitation of the tumor growth in a humanized murine model of peritoneal ovarian carcinosis. Furthermore, PDT using this new PS^{AF} seems to favor an activation of the immune response by inducing the secretion of effective cytokines and inhibiting the pro-inflammatory and immunosuppressive ones, as well as releasing extracellular vesicles (EVs) prone to activate immune cells. Finally, we show that PDT can activate CD4+ and CD8+ T cells resulting in a potential immunostimulating process.

Conclusion: All the results of this pilot study therefore indicate that targeted PS^{AF}-PDT treatment would not only be effective in rapidly and directly destroying target tumor cells, but would also promote the activation of effective immune response notably by EVs. These data thus open up good prospects for the treatment of micrometastases of intraperitoneal ovarian carcinosis that are currently inoperable.

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COP-12

Polymeric Encapsulation of a Ru(II) Polypyridine Complex for Cancer Targeted Photodynamic Therapy

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Over the last decades, photodynamic therapy (PDT) has received increasing attention as a complementary technique for the treatment of cancer. Among the investigated classes of photosensitizers, the use of Ru(II) polypyridine complexes is gaining increasing attention.[1] Despite the remarkable ability of many PDT agents, these compounds generally are associated with a poor cancer cell selectivity. As a consequence, high drug doses are needed, which can cause side effects.[2] To overcome this limitation, there is a need for the development of a suitable drug delivery system to increase the amount of photosensitizer delivered to the tumor. Herein, we report on a dual tumor targeting strategy based on the combination of (1) a passive targeting strategy with a polymer which can target tumorous tissue by the enhanced permeability and retention effect and (2) an active targeting strategy with the conjugation to biotin which is majorly taken up by the in a variety of cancerous cells overexpressed sodium multivitamin transporter. Based on this design, the nanoparticles showed much higher selectivity for cancer cells in comparison to non-cancerous cells in a 2D monolayer and 3D multicellular tumor spheroid model. Upon intravenous injection, an improved accumulation of the nanoparticles inside the tumour of a mouse compared to the Ru complex itself was determined. The nanoparticles were found to have a high phototoxic effect upon 1-photon (500 nm) or 2-photon (800 nm) excitation with an eradication of an adenocarcinomic human alveolar basal epithelial tumour inside a mouse model. These results suggest that the presented encapsulation method holds great potential for the development of cancer targeted PDT.[3]

References

[1] S. Monro, K. L. Colón, H. Yin, J. Roque, P. Konda, S. Gujar, R. P. Thummel, L. Lilge, C. G. Cameron, S. A. McFarland, *Chem. Rev.* **2019**, *119*, 797-828
[2] A. M. Bugaj, *Photochem. Photobiol. Sci.*, **2011**,*10*, 1097-1109.
[3] J. Karges, J. Li, L. Zeng, H. Chao, G. Gasser, *ACS Appl. Mater. Interfaces* **2020**, *12*, 54433-54444.

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In vitro efficacy *of* Zinc (II) Phthalocyanine for The Photodynamic Therapy of Human Melanoma Cancer

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Photodynamic therapy (PDT) is a non-invasive treatment method compared to conventional cancer treatments, and its damage is localized due to the high accumulation of phthalocyanines in the tumor area. For this reason and PDT has limited side effects in the surrounding tissues[1]. Compared to traditional antitumor treatments, PDT has the advantages of being a non-invasive treatment, showing a localized effect and causing little damage to healthy cells and tissues[2]. This study aims to investigate the PDT effects on MeWo (human melanoma cells) and HaCaT (normal human keratinocyte cells) using different light doses and concentrations of ZnPc. The cytotoxicity results have shown that HaCaT cell viability is not over-changed using ZnPc or ZnPc-PDT when ZnPc or ZnPc-PDT exhibited strongly cytotoxic effects on the MeWo cells. As a result, the HaCat cell line is not affected by either ZnPc or ZnPc-PDT. On the other hand, the MeWo cell is successfully treated with PDT when determined a certain dose of light and concentration of ZnPc (50 J/cm^2, 12.5 µM) were used. In this study similar to Ogbado's work, ZnPc-PDT indicates significantly high levels of late-apoptosis on the MeWo cells[3]. These findings are supported by the results of apoptosis with the Annexin V & Dead Cell Kit and fluorescence imaging.

References

(1) Allegra, A.; Pioggia, G.; Tonacci, A.; Musolino, C.; Gangemi, S. Oxidative Stress and Photodynamic Therapy of Skin Cancers: Mechanisms, Challenges and Promising Developments. *Antioxidants* **2020**, *9* (5), 1–20. https://doi.org/10.3390/antiox9050448.

(2) Zhang, L.; Ji, Z.; Zhang, J.; Yang, S. Photodynamic Therapy Enhances Skin Cancer Chemotherapy Effects through Autophagy Regulation. *Photodiagnosis Photodyn. Ther.* **2019**, *28* (April), 159–165. https://doi.org/10.1016/j.pdpdt.2019.08.023.

(3) Ogbodu, R. O.; Nitzsche, B.; Ma, A.; Atilla, D.; Gürek, A. G.; Höpfner, M. Photodynamic Therapy of Hepatocellular Carcinoma Using Tetra-Triethyleneoxysulfonyl Zinc Phthalocyanine as Photosensitizer. *J. Photochem. Photobiol. B Biol.* **2020**, *208* (October 2019), 111915. https://doi.org/10.1016/j.jphotobiol.2020.111915.

The 5th Photodynamic Day

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Synthesis and structure of meso-substituted [20π]-dibenzihomoporphyrins

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A series of bench-stable meso-substituted [20π]-dibenzihomoporphyrins have been synthesized via acid-catalyzed condensation of dipyrrole derivatives with aryl aldehydes[1]. The insertion of a 1,1,2,2-tetraphenylethene (TPE) or but-2-ene-2,3-diyldibenzene unit in the porphyrin framework resulted in the formation of [20π]-dibenzihomoporphyrins, combing the features of hydrocarbons and porphyrins. The meso substituents such as phenyl or methyl groups at the vinylene bridge and aryl substituents at the meso positions help control the conformational and electronic properties of such macrocycles.

To compare the structural and electronic features, di(p-benzi)homoporphyrins and di(*m*-benzi)homoporphyrins were synthesized by introduction of a *p*- or *m*-phenylene unit into the porphyrin framework. Single crystal X-ray analyses showed the non-planar structural details of the molecules, with the phenylene rings projecting out of the mean plane, defined by the dipyrromethene moiety and the two meso-carbon atoms. Spectroscopic and structural investigations showed that these macrocycles exhibit characteristics of both TPE and but-2-ene-2,3-diyldibenzene and dipyrromethene units indicating the non-aromatic characteristics of the compounds synthesized.

Additionally, a potential use of these dibenzihomoporphyrins as photosensitizers (PS) for photodynamic therapy (PDT) has been envisioned as they tend to produce singlet oxygen under illumination as detected via the degradation of 1,3-diphenylisobenzofuran (DPBF).

References

1. Grover, N., Emandi, G., Twamley, B., Khurana, B., Sol, V., Senge, M.O. Synthesis and Structure of meso-Substituted Dibenzihomoporphyrins. *Eur. J. Org. Chem.*, **2020**, *2020*, 6489-6496.

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Antimicrobial photosensitizers and their formulations: A potential solution to current world scenario

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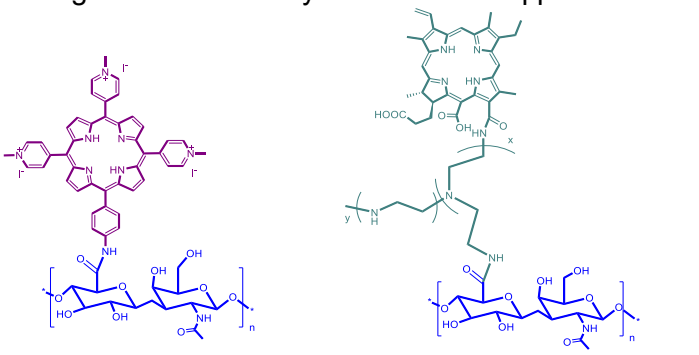
In order to provide a long-lasting solution to infections affecting the current world scenario, photodynamic therapy (PDT) offers a means to destroy pathogenic microbes via formation of reactive oxygen species, promoting the damage of microbial targets such as nucleic acids (DNA or RNA), proteins, lipids, protein complexes, or by impeding the biofilm matrix.[1]

Thus, the main aim of the study is to design and synthesize photoactive moieties based on porphyrin and chlorin macrocycles and BODIPY dyes for antimicrobial photodynamic therapy (aPDT).[2] Furthermore, incorporating these photo-moieties into biopolymeric hydrogels as shown in Figure 1 for a variety of biomedical applications are targeted.



Cationic; 5-(4-Acetamidophenyl)-10,15,20- tris(4-N-methylpyridinium) porphyrin covalently bonded with hyaluronic acid polymeric platform

Purpurin-18 covalently bonded with hyaluronic acid polymeric platform

Figure 1. Photosensitizers incorporated in a hyaluronic acid hydrogel matrix for aPDT applications.

Porphyrin based cationic photosensitizers (PSs) were synthesized and a chlorin based PS was extracted from *Spirulina maxima* and modified to be included on a biopolymeric hyaluronic acid hydrogel platform. This platform was characterized spectroscopically and evaluated for antimicrobial photoactivity via microbial evaluation on different gram strains of bacterial species. Singlet oxygen production was determined as well to evaluate the photoactivity of this polymeric hydrogel platform.

Furthermore, BODIPY dye-based PS species have been synthesized and modified for their activity as aPDT agents. Several *N*-heterocyclic BODIPY-dyes have been positively charged or functionalized for incorporation into hydrogel platforms. These dyes exhibit

good water solubility. A library of such *N*-heterocyclic BODIPY dyes was prepared and characterized and will be evaluated for photoactivity against microbes.

References

1. de Melo, W. C., Avci, P., de Oliveira, M. N., Gupta, A., Vecchio, D., Sadasivam, M., Chandran, R., Huang, Y. Y., Yin, R., Perussi, L. R., Tegos, G. P., Perussi, J. R., Dai, T., Hamblin, M. R. Photodynamic inactivation of biofilm: taking a lightly colored approach to stubborn infection. *Expert review of anti-infective therapy*, **2013**, *11*, 669-693.
2. Wiehe, A., O'Brien, J.M., Senge, M.O. Trends and targets in antiviral phototherapy, Photochem. Photobiol. Sci., **2019**,*18*, 2565-2612.

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Investigation of the impact of atropisomerism on Redaporfin photodynamic therapy efficacy

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Atropisomerism presents an intriguing, often neglected, source of structural variety in drug development. Such diversity in tetrapyrrole structures may enhance photosensitizer development for photodynamic therapy (PDT) and related drug developments. The present work demonstrates that the photosensitizer redaporfin (and related pre-cursor porphyrin molecules) atropisomers can be separated, do not interconvert at room temperature, and exert different biological effects. Redaporfin, a pre-clinical synthetic sulfonamide fluorinated bacteriochlorin, presents ideal properties for studying PDT including enhanced photostability and strong absorption at 750 nm. Hindered rotation of the C_m-aryl-macrocyclic bonds of the bacteriochlorin and porphyrin structures results in different spatial orientations of the sulfonamide groups in the meta positions. They are defined as: α_4 when all of the sulfonamide substituents of the phenyl groups are on the same side of the macrocycle plane; $\alpha_3\beta$ when three of the sulfonamides are on the same side of the plane and one is on the opposite side; $\alpha_2\beta_2$ when two sulfonamide groups are on each side and adjacent to each other and finally, $\alpha\beta\alpha\beta$ when two sulfonamides are on each side but alternate in the positions with respect to the macrocycle. Although the photo- and physicochemical properties of the four atropisomers are similar, their therapeutic efficacies are dramatically different. In vitro studies have demonstrated significant variability of the atropisomer phototoxicity and cellular internalization levels. In particular, the α_4 atropisomer has displayed the highest levels of uptake and phototoxicity. Atropisomers have presented similar mechanisms of cellular uptake, primarily passive diffusion with subcellular localization in the endoplasmic-reticulum-Golgi complex. Heightened α_4 internalization by cells of the tumor microenvironment has been observed in vivo. Efficacy studies have indicated that atropisomer activity varies in vivo when sufficient time for photosensitizer tumor cell internalization occurs. A better understanding of how atropisomerism impacts therapeutic effects may contribute to the establishment of enhanced drug development strategies.

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Unsymmetrical cationic porphyrin-cyclodextrin dyes for photoinactivation of *Escherichia coli*

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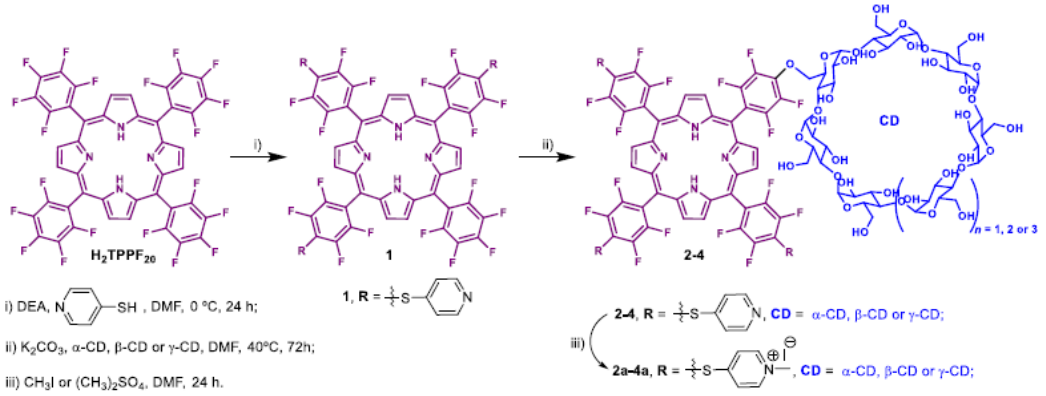
Microbial resistance is one of the scourges of the 21st century, being necessary to find new alternatives to the conventional therapeutics (e.g., antibiotics).[1-2] Photodynamic inactivation (PDI) of microorganisms arises as a new therapeutic approach widely studied and is based on the combination of three elements: photosensitizer (PS), dioxygen (O_2) and light. During this process, reactive oxygen species (ROS) are produced to kill rapidly and efficiently several microorganisms.[3] Unsymmetrical cationic porphyrins have been exploited as efficient PS for PDI of bacteria, viruses, or fungi.[4] Following our interests in PS development for PDI, we devote our efforts to the preparation of unsymmetrical cationic porphyrin-cyclodextrin conjugates (**2a-4a**) and to assessment of their photodynamic properties towards the photoinactivation of a Gram negative bacterium, *Escherichia coli*.



References

1. Hamblin, M. R., *Current opinion in microbiology* **2016**, *33*, 67-73.
2. Ribeiro, C. P. S.; Gamelas, S. R. D.; Faustino, M. A. F.; Gomes, A. T. P. C.; Tomé, J. P. C; Almeida, A.; Lourenço, L. M. O., *Photodiagnosis and Photodynamic Therapy* **2020**, *31*, 101788.
3. Calmeiro, J. M. D.; Dias, C. J.; Ramos, C. I. V.; Almeida, A.; Tome, J. P. C; Faustino, M. A. F.; Lourenco, L. M. O., *Dyes and Pigments* **2020**, *173*, 107410.
4. Vieira, C.; Santos, A.; Mesquita, M. Q.; Gomes, A. T. P. C.; Neves, M. G. P. M. S.; Faustino, M. A. F.; Almeida, A., *Journal of Porphyrins and Phthalocyanines* **2019**, *23* (04n05), 534-545.

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Nanoarchitectures for enhanced singlet oxygen generation

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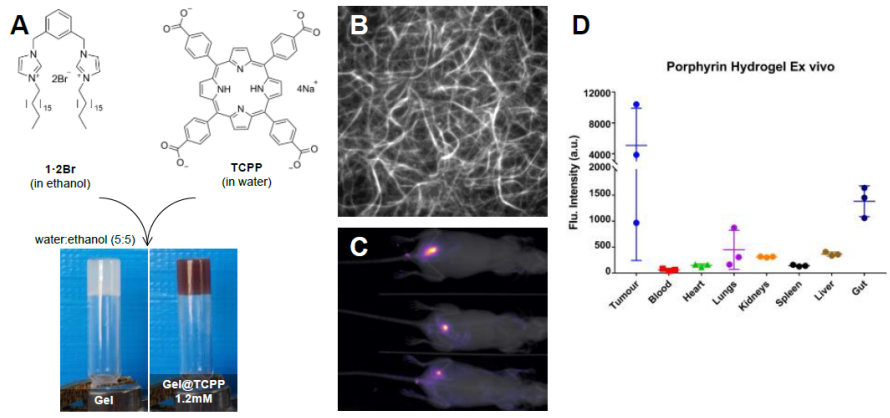
Nanostructured materials[1] are extensively studied because their novel properties enable challenging applications in all fields of science. However, the exact influence of their supramolecular structure on their properties remains poorly understood. We have prepared and characterized nanostructured materials such as bio-functionalized silicon microparticles[2], inorganic and metallic nanoparticles[3] and supramolecular hydrogels[4] designed for biological applications as sensing and delivering to living cells, with particular attention to their potential use in photodynamic therapy. One of our more recent findings arises from the incorporation of photosensitizers (PS) into supramolecular hydrogels[5] (Figure) as well as their immobilization onto polysilicon microparticles[6], showing that the supramolecular organization improves the SO generation with respect to solutions of the parent PS. Moreover, preliminar in-vivo studies show that the photosensitizer is localized in the tumour to a much higher extent than in other organs. The enhancement in SO generation induced by this type of hybrid material makes it an attractive candidate to be used in different applications when efficient SO production is required.



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Novel multi-stimulus responsive nanoparticles for intraoperative NIR imaging and treatment of pancreatic cancer

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Pancreatic cancer (PC) is ranked amongst the most lethal forms of cancer. Currently, for patients with locally advanced disease, surgical resection represents the only practical approach for the management of PC. In order to extend the limits of tumour resectability, image-guided surgery offers a valid tool to accurately delineate the borders of the tumour and facilitate surgical resection. Moreover, near-infrared (NIR) laser treatment of the resection site immediately after tumour removal can help destroy residual microscopic tumour fragments and prevent their proliferation after surgery. In this regard, our research group has developed a novel multi stimulus-responsive nanoparticle formulation containing indocyanine green (ICG), a clinically approved NIR fluorescent agent with photothermal properties. In a previous work poly-l-glutamic acid (PGA) was used as the carrier polymer.[1] In this work PGA was modified by partial conjugation of the carboxylate side groups with a lipid molecule, which resulted in the formation of nanoparticles with increased ICG-loading yield. In order to demonstrate the multi-stimulus nature of the new nanoparticle formulation, fluorescence studies were carried out at pH 7.4 and 6.4, and in the absence or in the presence of the proteolytic enzyme Cathepsin B (CB). Although ICG fluorescence was quenched within the nanoparticles, fluorescence recovery was observed after 24 hours upon nanoparticle digestion by CB with the highest fluorescence signal at pH 6.4. CB is overexpressed in advanced PC and its production and activity are particularly enhanced at the tumour acidic pH. Therefore, these promising preliminary results suggest that this novel nanoparticle formulation has the potential to exploit the microenviroment characteristics of PC to selectively release ICG at the tumour site for intraoperative imaging and treatment.

References

1. Tarassoli S; Martinez de Pinillos S; Pye H, Mosse CA; Callan JF; Macrobert S, McHale AP; Nomikou N. Cathepsin B-degradable, NIR-responsive nanoparticulate platform for target-specific cancer therapy. *Nanotechnology* **2017**;28(5),055101.

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Transition Metal Complexes in Phototherapy: Computational Insights

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The medical techniques based on the use of light for activating the drug are occupying a prominent place in the cancer treatment due to their selectivity that contributes to reduce undesirable side effects of conventional chemotherapy. Among these therapeutic treatments, photodynamic therapy (PDT) and photoactivated chemotherapy (PACT) are emerging as complementary approaches for selective destruction of neoplastic tissue through direct cellular damage. Both techniques rely on the employment of a molecule, photosensitizer PS, able to absorb within the so-called therapeutic window (500-850 nm). Thus, the exposure to light of otherwise inert molecules promotes the population of excited states of the drug, that in PDT are able to produce the cytotoxic species, such as $^1O_2$ and other ROS, in PACT can be responsible of the active species release or formation (Figure 1).

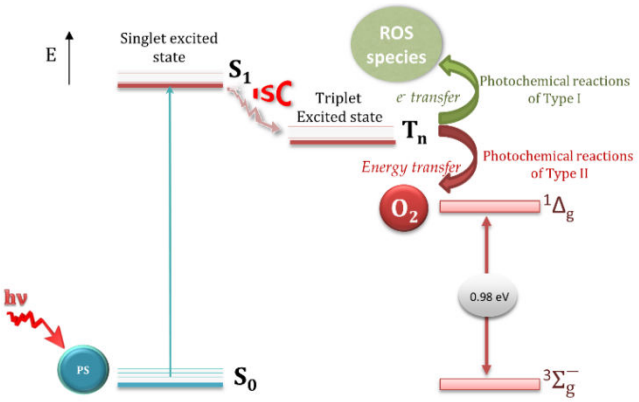

Figure 1

Following the success of cisplatin in conventional treatments, many other transition metal complexes were explored as anticancer agents for applications in different medical approaches, including PDT and PACT, in order to improve their chemical, biological and photophysical properties. The understanding of the photodynamic mechanism and the design of new effective therapeutic agents can take important advantages from theoretical computations capable to enlighten the key structural and photophysical features affecting the performance of the photosensitizer.[1-3]

References

1. Alberto, M. E.; Mazzone, G.; Regina, C.; Russo, N.; Sicilia, E. Theoretical exploration of the photophysical properties of two-component Ru II–porphyrin dyes as promising assemblies for a combined antitumor effect. *Dalton Transaction,* **2020**, *49, 12653*.
2. Dabbish, E.; Mazzone, G.; Russo, N.; Sicilia. E. Mechanism of action of the curcumin cis-diammineplatinum (ii) complex as a photocytotoxic agent. *Inorg. Chem. Front.*, **2020**, *7*, 2759
3. De Simone, B. C.; Mazzone, G.; Sang-aroon, W.; Marino, T.; Russo, N.; Sicilia, E. Theoretical insight into joint photodynamic action of a gold (I) complex and a BODIPY chromophore for singlet oxygen generation. *Phys. Chem. Chem. Phys.*, **2019**, *21*, 3446

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Synthesis and cellular properties of a 13^1-substituted chlorin e_6-nevirapine conjugate

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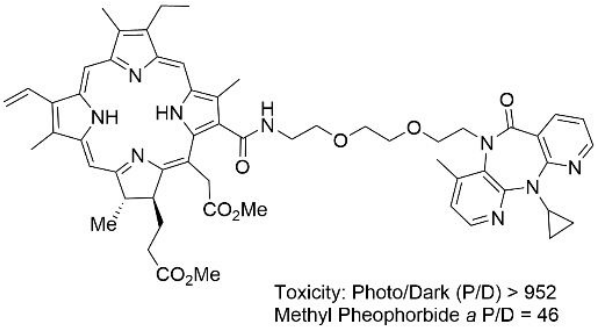
A chlorin e_6-nevirapine conjugate was prepared through the conjugation of nevirapine moiety on the 13^1-position of chlorin e_6 via a diethylene glycol linker. This conjugate was highly phototoxic (IC_{50} = 0.21 μM at 1 J/cm^2) toward human HEp2 cells, but non-toxic in the dark (IC_{50} > 200 μM). The photo/dark toxicity ratio of this conjugate is around 20 times larger than the ratio of methyl pheophorbide a. The chlorin e_6-nevirapine conjugate accumulated within cells in multiple organelles, including the Golgi, lysosomes, and mitochondria.



Toxicity: Photo/Dark (P/D) > 952
Methyl Pheophorbide *a* P/D = 46

References

1. Zhang, G., Wang, M., Collins, B. R., Vicente, M. G. H., Smith, K. M., Synthesis and cellular properties of a 13^1-substituted chlorin e_6-nevirapine conjugate. *J Porphyr Phthalocyanines.* **2021**, Just accepted manuscript.
2. Dong, J. J., Zhou, Y., Liu, Y. T., Zhang, Z. W., Zhou, X. J., Wang, H. J., Liao, L., In vitro evaluation of the therapeutic potential of nevirapine in treatment of human thyroid anaplastic carcinoma. *Mol. Cell. Endocrinol.* **2013**, *370*, 113-118.

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The X-ray-induced photodynamic effect of AGuIX@Terbium-porphyrin nanoparticle can be substituted by Galium-68.

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X-ray-induced Photodynamic Therapy (X-PDT) is an alternative strategy to improve Photo Dynamic Therapy (PDT) for cancer treatment[1] PDT consists in the transfer of light-photon to a photosensitizer which in turn produces singlet oxygen and reactive species. The photo reactions depend mainly on the photosensitizer, light and the presence of molecular oxygen. The X-PDT principle is based on the conversion of X-ray photons into visible photons, from a so-named nanoscintillator embedded in nanoparticles (NPs) and linked to the photosensitizer, which, in turn, produces singlet oxygen and reactive. species. Recently, several lines of evidence demonstrated that radionuclides can be used instead of X-rays irradiation to produce similar photodynamic effect, using NPs containing both nanoscintillator and photosensitizer. The obtained results are related to the Cerenkov luminescence and it is based on the emission of $\beta+$ positrons during lifetime disintegration of the radionuclides[2].
The ultra-small Gadolinium (Gd) based nanoparticle, namely AGuIX®, were initially designed for a non-toxic resonance magnetic agent and for its imaging properties[3]. Recently, we replaced Gd from the AGuIX@ platform by Terbium and added 5-(4-carboxyphenyl succinimide ester)-10,15,20-triphenylporphyrin (P1) [4]. The new NP, referred as AGuIX@Tb-P1, was characterized for its photo-physical and biological properties. We demonstrated that the NP design is compatible for X-PDT. Using U251 MG human glioblastoma cells, we showed that AGuIX@Tb-P1 pre-treated cells exposed to X-rays underwent cell growth arrest with an enhanced factor of 35%, when compared to results of untreated cells exposed to X-rays[4].
Based on our previous results, we assessed whether Galium-68 (^{68}Ga) could be used in order to substitute X-ray irradiation, using the same experimental procedure as previously described[4]. Thus, U251 MG cells were treated with AGuIX@Tb-P1 or the same NP without P1 for 24 h, before addition of increase doses of ^{68}Ga (0.1-1 MBq) in the cell medium for another 24h-delay. U251 MG cells were also pre-treated with the original AGuIX@Gd associated with P1. We showed i) that ^{68}Ga-mediated Cerenkov luminescence is sufficient to transfer photon to AGuIX@Tb-P1, whose produce P1-mediated singlet oxygen; ii) U251 cell clone formation decreased when the cells are pre-treated with AGuIX@Tb-P1 and exposed to ^{68}Ga; iii) the effect on cell clone formation

was close when cells were pre-treated with AGuIX@Tb-P1 and exposed either to X-rays at a dose of 3.0 Gy.min-1 or to 1 MBq ^{68}Ga added to cell medium.
Therefore, ^{68}Ga could substitute X-ray irradiation to improve photodynamic treatment against cancer cells, using NPs initially designed for X-PDT.

Bibliography

[1]. Larue L *et al.* Using X-rays in photodynamic therapy: An overview. Photochem. Photobiol. Sci. 2018, 17, 1612–1650, doi:10.1039/c8pp00112j.
[2]. Daouk J *et al*. Does Cerenkov light really induce effective photodynamic therapy? A short review and a theorical reflexion. Radiation 2021,1, 5–17; doi:10.3390/radiation1010002.
[3]. Mignot A *et al.* top-down synthesis route to ultrasmall multifunctional Gd-based silica nanoparticles for theranostic applications. Chemistry 2013, 19, 6122–6136.
[4]. Daouk J *et al.* Terbium-based AGuIX-design nanoparticle to mediate X-ray-induced photodynamic therapy. Pharmaceuticals 2021,14, 396, doi:10.3390/ph14050 396.

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Antimicrobial Photodynamic Therapy in biofilm *Staphylococcus aureus*.

Isabelle de Paula Ribeiro[a], Juliana Teixeira Pedroso[a], Beatriz Muller Nunes Souza[a] , Juliana Guerra Pinto[a] and Juliana Ferreira-Strixino[a]

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Staphylococcus aureus are superbacteria that cause great concern in hospitals due to their high virulence and resistance to antibiotics[1]. The most alarming virulent form of this species is biofilm, characterized by the set of microorganisms adhered to a surface that are surrounded by an extracellular polymeric matrix. In the hospital environment, this species forms biofilms in catheters and tubes, causing serious infections, which can lead to sepsis.[2]. A Antimicrobial Photodynamic Therapy (APDT) is presented as a promising alternative against *S. aureus* infections [3,4]. The study aimed to evaluate the action of APDT on biofilm of *S. aureus* by Scanning Electron Microscopy (SEM). The strains of *S. aureus* were grown in Brain Heart Infusion medium for 24 h at 37°C. Biofilms were formed in laminules during 48h. Then, curcumin was incubated at a concentration of 100 µg/ml and APDT was applied with irradiation at 450 nm, light dose of 100 J/cm² and intensity of 110mW. After irradiation, the samples were fixed, dehydrated in growing alcohol solutions and incubated in the greenhouse for 24 h. After metallization, the samples were analyzed by SEM. In the obtained results it was possible to observe that the control group, maintained in the absence of light, formed biofilm, whereas the groups only photosensitizer, only light and the APDT group showed a decrease in colonies, that is, antibiofilm activity. It is concluded that the therapy demonstrated to have effective antimicrobial activity, however the parameters of irradiation and concentration of the photosensitizer should be studied, since isolates have influenced the adherence of the colonies as well as the TFDa group.

References:

1. Hultén KG, Mason EO, Lamberth LB, Forbes AR, Revell PA, Kaplan SL. Analysis of Invasive Community-Acquired Methicillin-Susceptible Staphylococcus aureus Infections During a Period of Declining Community Acquired Methicillin-Resistant Staphylococcus aureus Infections at a Large Children's Hospital. *Pediatr Infect Dis J*. 2018;37(3):235–241. doi:10.1097/INF.0000000000001753.
2. Lima MFP, Borges MA, Parente RS, Júnior RCV, Oliveira ME De. *Staphylococcus aureus* e as ınfecções hospıtalares – revısão de lıteratura. *Uningá*. 2015;21(1):32–39. http://www.mastereditora.com.br/review.
3. Freitas MA, Pereira AH, Pinto JG, Casas A, Ferreira-Strixino J. Bacterial viability after antimicrobial photodynamic therapy with curcumin on multiresistant *Staphylococcus aureus*. *Future Microbiol*. 2019;14(9):739–748. doi:10.2217/fmb-2019-0042
4. Quishida CCC, Carmello JC, Mima EG de O, Bagnato VS, Machado AL, Pavarina AC. Susceptibility of multispecies biofilm to photodynamic therapy using Photodithazine®. *Lasers Med Sci*. 2015;30(2):685–694. doi:10.1007/s10103-013-1397-z.

The 5th Photodynamic Day

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Cationic versus anionic phthalocyanines for photodynamic therapy: What a difference the charge makes

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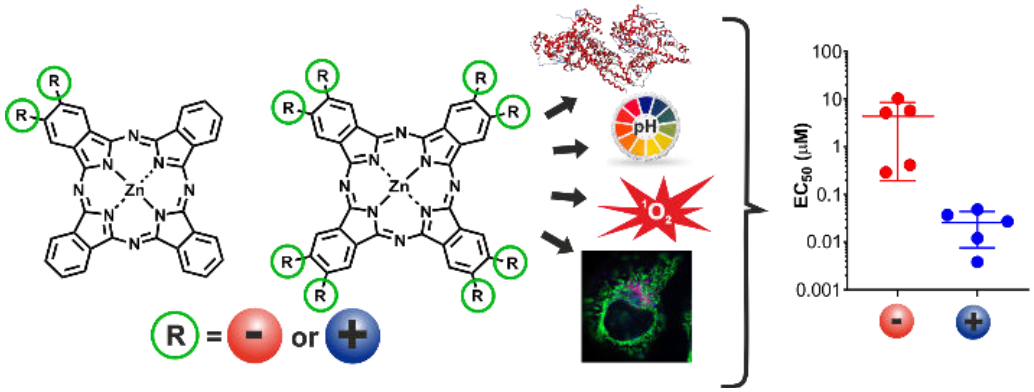
Phthalocyanines (Pcs) and their aza-analogues represent a promising group of organic dyes with interesting photophysical properties (strong absorption in area over 600 nm and strong singlet oxygen production) highly suitable for the use in photodynamic therapy of cancer. The literature reports on anionic and cationic Pcs for photodynamic therapy suggest systematically significant differences in their photodynamic activity.

In this work, ten different zinc (II) Pcs bearing carboxylate function or quaternary nitrogens were investigated for photophysical, physicochemical, binding and biological properties with the aim of finding the parameters and/or factors that may contribute to the substantial difference in photodynamic activity between Pcs bearing opposite charges on peripheral substituents.

Four different sets of compounds were introduced into the study, namely anionic hydrophilic, cationic hydrophilic, anionic amphiphilic, and cationic amphiphilic to compare both the influence of the charge type and its distribution on the macrocycle core.

All Pcs were tested on photodynamic activity *in vitro* on HeLa cells with different activity for anionic Pcs (EC_{50} ~ 0.3-10 μM) and cationic Pcs (EC_{50} ~ 3-50 nM). The effect of pH, binding to serum proteins, interaction with biomembranes, subcellular localization and relocalization after irradiation were disclosed to be the main factors responsible for lower photoactivity of anionic Pcs.[1]

The work was supported by Czech Science Foundation (19−14758Y) and Charles University (projects SVV 260 547 and PRIMUS/20/SCI/013).



References
1. Kollar J. et al. *Journal of Medicinal Chemistry. 2020; 63*(14): 7616-7632.

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Radiolabelled Theranostic Agents in Cellulose Nanocrystals

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Cancer is one of the biggest set of diseases to concern our society, meaning that an urgent need of new drugs and practices to treat it is needed. Early diagnosis undertakes, alongside treatment, a critical role for the desired effect. In this case, imaging is an extremely intriguing tool since it allows not only for diagnosis but to follow treatment as well. We have synthesized and radiolabeled photo-responsive molecules in cellulose nanocrystals, therefore creating theranostic agents. Several steps have been taken to synthesize these PDT agents and to radiolabel them for diagnostic purposes using SPECT imaging. First, photo-responsive molecules were prepared[2] and characterized. These were then used to construct metalla-assemblies through coordination with ruthenium dimers.[3] They were subsequently linked to CNCs[4] for better solubility, targeting, and transport to biological targets. The resulting photo-responsive compounds were then radiolabeled with technetium-99m, allowing them to also be used as imaging probes. After synthesis, *in vitro* assays were performed to determine the IC_{50} and whether the PDT agents were selective towards cancer cell lines. Finally, radiolabelling with technetium-99m and administration of these compounds in SCID mice allowed to follow their biodistribution for 24h through SPECT imaging, showing preferential accumulation in the liver for non-tumor bearing mice. The *in vitro* and *in vivo* data confirmed that these compounds are interesting agents for PDT, and so we are able to conclude that we have achieved a multimodal agent combining an optimized theranostic agent for PDT treatment. Lastly, more *in vivo* experiments are currently being performed to confirm that such molecules can be used for the imaging of solid tumors, which would allow them to be used for diagnostic purposed as well.

References

1. Robertson, C. A.; Evans, D. H.; Abrahamse, H. Photodynamic Therapy (PDT): A Short Review on Cellular Mechanisms and Cancer Research Applications for PDT. *Journal of Photochemistry and Photobiology B: Biology*. **2009**, *96*, 1–8.
2. Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. A Simplified Synthesis for Meso-Tetraphenylporphine. *The Journal of Organic Chemistry.* **1967**, *32*, 476.
3. Mannancherril, V.; Therrien, B. Strategies Toward the Enhanced Permeability and Retention Effect by Increasing the Molecular Weight of Arene Ruthenium Metallaassemblies. *Inorganic Chemistry.* **2018**, *57*, 3626–3633.
4. Chauhan, P.; Hadad, C.; Sartorelli, A.; Zarattini, M.; Herreros-López, A.; Mba, M.; Prato, M.; Prato, M.; Carofiglio, T. Nanocrystalline Cellulose–Porphyrin Hybrids: Synthesis, Supramolecular Properties, and Singlet-Oxygen Production. *Chemical Communications.* **2013**, *49*, 8525–8527.

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Imidazole substituted phthalocyanines

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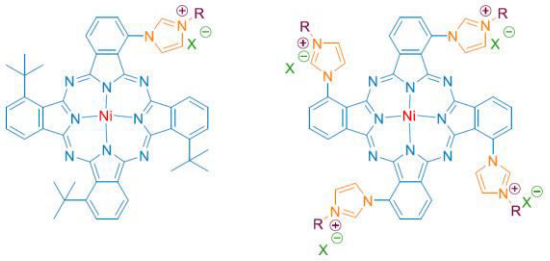
Phthalocyanines, which are chemically and thermally highly stable, are synthesized on a wide scale for many application areas. Due to their interesting physical and chemical properties, phthalocyanines have the potential to be used in many areas such as catalysts[1], sensors[2], photodynamic therapy[3], are widely used in these fields. The substituents existing in phthalocyanines have a great effect on the application areas. Imidazole substituted molecules have been interesting for their optical, electronic and catalytic properties [4-6]. In addition to the limited number of imidazole substituted phthalocyanines found in the literature, this study aimed to prepare mono and tetra imidazole substituted phthalocyanines. The synthesis of novel imidazole-substituted mono and tetra-phthalocyanine complexes and their quaternary derivatives as a result of the quaternization reaction of these complexes with methyl, hexyl and dodecyl halides have been reported. All compounds synthesized including phthalonitrile were synthesized for the first time within the scope of this study, and all of them are unique molecules. These complexes were characterized by FT-IR, MALDI-MS and UV-vis spectroscopic techniques. The aggregation and electronic properties of imidazole-substituted tetra-phthalocyanine complexes have been studied using different solvent systems and interesting results have been obtained. As a result, within the scope of this study, original molecules were synthesized, and their electronic properties were studied using UV-vis spectroscopy using different solvent mixtures.



References

1. Alexander B. Sorokin. Phthalocyanine Metal Complexes in Catalysis. Chemical Reviews **2013**, *113*(10), 8152–8191.
2. Denisha Gounden, Nolwazi Nombona, Werner E. van Zyl. Recent advances in phthalocyanines for chemical sensor, non-linear optics (NLO) and energy storage applications. Coordination Chemistry Reviews **2020**, *420*, 213359.
3. Pui-Chi Lo, M. Salome Rodrıguez-Morgade, Ravindra K. Pandey, Ng, Dennis K. P. Ng, Tomas Torres, Fabienne Dumoulin. The unique features and promises of phthalocyanines as advanced photosensitisers for photodynamic therapy of cancer. Chemical Society Reviews **2020**, *49*, 1041-1056.
4. Jian-Yong Liu, Pui-Chi Lo, Dennis K.P. Ng. Phthalocyanine-Containing Supramolecular Arrays. Structure and Bonding **2010**, *135*, 169–209.
5. Akiharu Satake, Yoshiaki Kobuke. 'Artificial Photosynthetic Systems: Assemblies of Slipped Cofacial Porphyrins and Phthalocyanines Showing Strong Electronic Coupling. Organic & Biomolecular Chemistry **2007**, *5*(11), 1679.
6. Yoshiaki Kobuke. Artificial Light-Harvesting Systems by Use of Metal Coordination. European Journal of Inorganic Chemistry **2006**, *12*, 2333–2351.

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New anti-inflammatory and pro-apoptotic photosensitizers against arthritis

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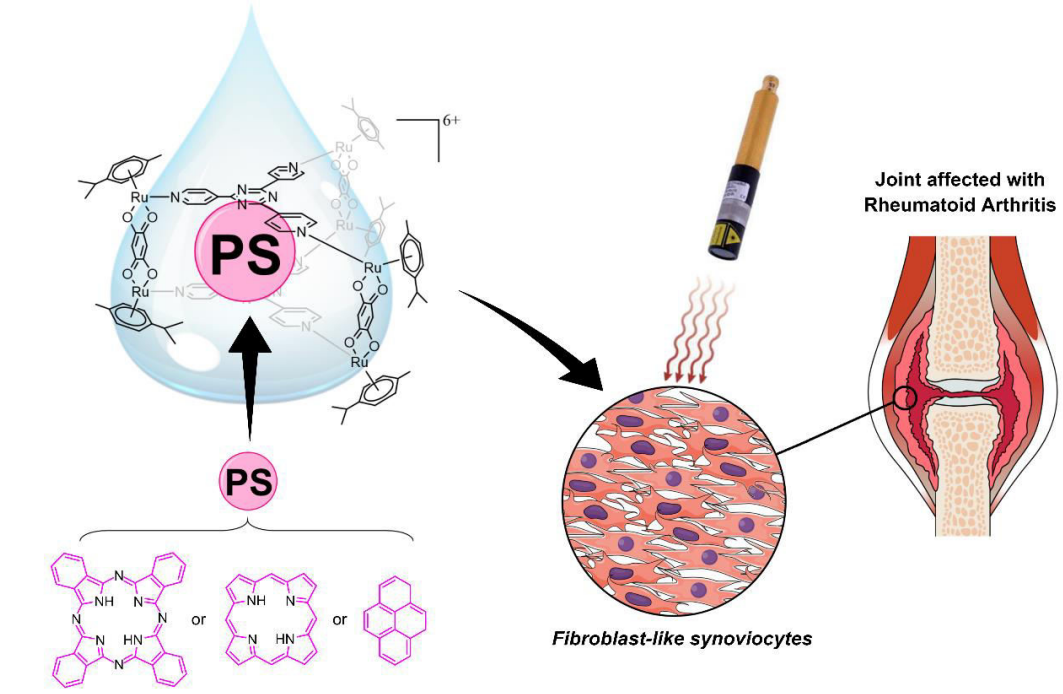
Contrary to popular belief, rheumatoid arthritis (RA) is not a disease only associated with aging, since it can also affect young people.[1] It is an autoimmune pathology that, although mainly affecting joints, can also attack other organs such as kidneys, lungs or heart. If left untreated, it can lead to a serious prognosis.[2] The most common treatment remains synovectomy, which is an invasive treatment and involves long periods of postoperative rehabilitation. In recent years, promising results have been achieved using non-invasive treatments such as anti-tumor necrosis factor drugs, Janus kinase inhibitors, and especially photodynamic therapy (PDT).[3] The latter involves a photoactive compound, a photosensitizer (PS), and light activation. The simplicity and non-invasiveness make PDT an ideal treatment to alleviate the pain or disability caused by RA. Unfortunately, conventional PSs often have some drawbacks related mainly to their low solubility in biological media and undesirable side effects such as light hypersensitivity.[4] We believe that it may be possible to solve the poor water solubility of PSs using ruthenium metallacages. These metallacages are soluble in biological media and have an inner cavity in which the PS can lodge. Such ruthenium metallacages have already been tested *in vitro* on cancer cells, demonstrating their potential.[5]



Unsoluble PSs could be placed inside the cavity of the metallacage to transport it in biological media

We have now designed new ruthenium metallacages and tested them as PDT agents against RA. The *in vitro* activity of these PS carriers in human fibroblast-like synoviocytes cells (FLS) is promising. The proliferation assays are excellent, and now the anti-inflammatory and pro-apoptotic activity of ruthenium metallacages with different PSs are under investigation. Our most recent results will be presented.

References

[1] Stuart M.J., Rand J.A., *J. Bone Joint Surg*, **1988** 70, 84-87.
[2] Maradit-Kremers, H., Crowson, C.S., Nicola, P.J., Ballman, K.V., Roger, V.L., Jacobsen, S.J., Gabriel, S.E., *Arthritis Rheumatol*, **2005**, 52, 402-411.
[3] Gallardo-Villagrán, M., Leger, D. Y., Liagre, B., Therrien, B., *Int J Mol Sci*, **2019**, 20, 3339.
[4] Koderhold, G., Jindra, R., Koren, H., Alth, G., Schenk, G., *J Photoch Photobio B*, **1996**, 36, 221-223.
[5] Schmitt, F., Freudenreich, J., Barry, N. P., Juillerat-Jeanneret, L., Süss-Fink, G., Therrien, B., *J Am Chem Soc,* **2012**, 134, 754-757.

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What a difference the carrier makes – NMR to examine the intracellular fate of chlorin e4

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Background: The application of nanosized carrier systems has become an inevitable part in the delivery of porphyrinic photosensitizers (PSs) to their sites of action in photodynamic therapy (PDT). Multiple beneficial functions are fulfilled by the carrier including solubilization and stabilization of the PS, enriched or targeted uptake by the diseased tissue or providing nanoplatforms for combined theranostic agents.[1, 2] However, how the carrier affects the fate of the PS after cell uptake is still not well known. NMR spectroscopy offers a unique approach to study porphyrin interactions with their immediate physiologic environment on a molecular or even atomic level.[3]

Methods: Cultured HeLa cells were incubated in the dark and upon subliminal light irradiation with chlorin e4 (Ce4) with and without the Ce4-encapsulating carriers polyvinylpyrrolidone (PVP) and poloxamer micelles composed of Kolliphor P188 (KP).[4] The cells were then submitted to high resolution magic angle spinning (HR-MAS) NMR spectroscopy for studying the cell metabolic profile. Multivariate statistical methods, targeted metabolite analysis and diffusion editing techniques were applied.

Results: Principal component analysis (PCA) and partial least squares analysis (PLS) revealed a Ce4-concentration dependent metabolic response of HeLa cells. The metabolic response was clearly attenuated in the dark when Ce4 was combined with KP and even more with PVP. Spectral perturbation of phospholipid resonances indicated Ce4 membrane localization. Strong attenuation of this effect suggests that Ce4 remains associated with PVP inside the cells. Direct detection of KP-resonances combined with diffusion studies suggests that the micelles are internalized but partly disassembled.

Conclusion: The results underline the beneficial effect of carriers following cell internalization. In addition to the known advantages they attenuate the metabolic response reducing potential toxic effects in the dark while not compromising the phototoxic reaction. Micelles promote intracellular redistribution of PSs to membranes whereas PVP may retain the PSs. The impact on PDT efficiency remains to be evaluated in further studies.

References

1. Bechet, D.; Couleaud, P.; Frochot, C.; Viriot, M. L.; Guillemin, F.; Barberi-Heyob, M., Nanoparticles as vehicles for delivery of photodynamic therapy agents. *Trends in Biotechnology* **2008,** *26* (11), 612-621.
2. Obaid, G.; Broekgaarden, M.; Bulin, A. L.; Huang, H. C.; Kuriakose, J.; Liu, J.; Hasan, T., Photonanomedicine: a convergence of photodynamic therapy and nanotechnology. *Nanoscale* **2016,** *8* (25), 12471-12503.
3. Gjuroski, I.; Furrer, J.; Vermathen, M., Probing the Interactions of Porphyrins with Macromolecules Using NMR Spectroscopy Techniques. *Molecules* **2021,** *26* (7), 1942.
4. Gjuroski, I.; Girousi, E.; Meyer, C.; Hertig, D.; Stojkov, D.; Fux, M.; Schnidrig, N.; Bucher, J.; Pfister, S.; Sauser, L.; Simon, H.-U.; Vermathen, P.; Furrer, J.; Vermathen, M., Evaluation of polyvinylpyrrolidone and block copolymer micelle encapsulation of serine chlorin e6 and chlorin e4 on their reactivity towards albumin and transferrin and their cell uptake. *Journal of Controlled Release* **2019,** *316*, 150-167.

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Pheophorbide-a mediated photodynamic therapy induced cell death of prostate cancer with apoptosis pathway

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Backround: Photodynamic therapy (PDT) is a promising cancer treatment modality that using a photosensitizer which can be distributed into cancer cells and be activated by appropriate wavelength of light on the tumor site [1]. Activated photosensitizer could kill tumor cells in the presence of oxygen via producing reactive oxygen species especially singlet oxygen via apoptosis or other pathways [2]. In this study, we evaluated pheophorbie-a mediated photodynamic antitumor efficiency and possible apoptosis mechanism on prostate cancer cells.

Methods: PC3 and LNCaP cells were used to asses efficacy of pheophorbide-a mediated PDT. After seeded the cells, pheophorbide-a mediated PDT in different concentrations (0 μM, 0.1 μM, 0.2 μM, 0.5μM, 1 μM, and 5 μM) were used on prostate cancer cells. The cell proliferation in each group was measured by methyl thiazolyl tetrazolium (MTT) assay and clone and the cell apoptosis was detected via Hoechst33258 staining and Annexin V/propidium iodide (PI) double labeling. The expressions of apoptosis-related proteins (caspase 3, caspase, 8, caspase 9, Parp, Bcl2, Bax) were performed by using western blot methods. The reactive oxygen species were measured by Muse cell analyzer.

Results: MTT results showed pheophorbide-a mediated PDT decreased cell viability on prostate cancer cells. Hoechst and propidium iodide showed that the apoptotic cells were increased after treatment. Western blot images results showed that caspase 8, caspase 3, Parp and Bax levels were increased and caspase 9 and Bcl2 expressions were decreased. Reactive oxygen species levels were increased significantly after pheophorbide-a mediated PDT.

Conclusions: All together, our results showed that pheophorbide-a PDT decreased cell viability of prostate cancer via production reactive oxygen species and induced apoptotic pathways and appears to be a good candidate for prostate cancer PDT treatment.

Acknowledgements: This study was supported by the Aydın Adnan Menderes University Scientific Research Fund (grant number TPF-15068).

References

1.Triesscheijn M, Baas P, Schellens JH, Stewart FA. Photodynamic therapy in oncology. Oncologist 2006;11(Oct 9):1034—44

2. Bilgin MD, Aksel M, Değirmenci EH, Bozkurt-Girit M, Ozmen A. Efficacy of Methylene Blue and Aliminium Phthalocyanine MediatedSonophotodynamic Therapy on Prostate Cancer Cell Lines. Biophysical Journal 112(3):282a-283a.

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Delivery systems as a protection tool of magnesium phthalocyanines and tetrapyrazinoporphyrazines against demetallation in acidic media

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Magnesium complexes of phthalocyanines (Pc) and their azaanaloges (AzaPc) are widely examined as potential diagnostic and therapeutic dyes for their interesting photophysical properties.1 The instability of magnesium complexes in acidic environment (demetallation to metal-free ligands) causes the main obstacle to wider utilization of these dyes considering that majority of the dye is gathered in the cell's lysosomes. Due to demetallation macrocycles lose their strong photophysical properties irreversibly. This project evaluated more closely the demetallation process of these compounds at various pH. The inertness was monitored by absorption spectroscopy where characteristic splitting of the Q-band occurs after demetallation. Water-soluble compounds were tested in buffers at five different pH ranging 1 – 7.4. Lipophilic derivatives were tested mainly after incorporation into two delivery systems (liposomes and microemulsions). Both approved high level of protection. In liposomes no changes in absorption spectra of AzaPc were detected even after 24 h at the most acidic pH. Experiments proved that without any protection means the more acidic environment the faster process of the demetallation occurs. Moreover, magnesium complexes of AzaPcs are more stable than corresponding Pcs.

References

1. Novakova, v., Donzello, M. P., Ercolani, C., Zimcik, P., Stuzhin, P. A.: Tetrapyrazinoporphyrazines and their metal derivatives. Part II: Electronic structure, electrochemical, spectral, photophysical and other application related properties, Coord. Chem. Rev., **2018**, 361, 1-73.

2. Tuhl, A., Makhseed, S., Zimcik, P., Al-Awadi, N., Novakova, V., Samuel, J.: Heavy metal effects on physicochemical properties of non-aggregated azaphthalocyanine derivatives. J. Porphyrins Phthalocyanines, **2012**, 16, 817-825.

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Cationic tripyridylporphyrins and their Zn(II) complexes: a comparison of 645 nm with 605 nm light irradiation for PDT

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The use of cationic amphiphilic porphyrin-based photosensitisers (PSs) offers many advantages for photodynamic therapy (PDT).[1] In our previous work, cationic tripyridylporphyrins with the long alkyl chain showed an high PDT effect on five different tumour cell lines and on fibroblasts, as opposed to their analogues without the alkyl chain.[2] The increased lipophilicity led to an improved cellular uptake, however, a somewhat dark toxicity was observed as well as a lack of selectivity between normal and cancer cells. This prompted us to investigate the impact of alkyl chains of different length as well as metalation for the fine-tuning of lipophilicity.

It was shown with tetrapyridylporphyrins that Zn(II) chelation increases the triplet excited state lifetimes of the porphyrins and also has an effect on their lipophilicity, thus it may improve the PDT activity.[3] Although red light is commonly used for the anti-tumour PDT, orange light also falls under the optimal therapeutic window and may efficiently penetrate skin layers where melanoma occurs.[4] Furthermore, orange light could be more appropriate for photoexcitation of zinc porphyrins given their optical properties.

We will present the synthesis of free base *N*-methylated tripyrid-3-ylporphyrins with alkyl chains of different length (C8, C10, C16 and C18), and their Zn(II) analogues. Moreover, we will describe and compare their spectroscopic characteristics, lipophilicity, and singlet oxygen production, as well as their PDT activity on human melanoma cells (MeWo) and human foreskin fibroblasts (HFF). We will also compare the PDT activity of Zn(II) complexes after irradiation with orange (605 nm, fluence rate 1.5 mW/cm^2, fluence 2.7 J/cm^2) and red light (645 nm, fluence rate 2 mW/cm^2, fluence 3.6 J/cm^2).

References

1. Malatesti, N.; Munitić, I., Jurak. I. *Biophys. Rev.* **2017**, *9*, 149–168.
2. Jelovica, M.; Grbčić, P.; Mušković, M.; Sedić, M.; Kraljević Pavelić, S.; Lončarić, M.; Malatesti, N. *ChemMedChem* **2018**, *13*, 360-372.
3. Benov, L.; Craik, J.; Batinic-Haberle, I. *Anti-Cancer Agents Med. Chem*. **2011**, *11*, 233–241.
4. Kim, M. M.; Darafsheh, A. *Photochem. Photobiol*. **2020**, *96*, 280–294.

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Nanodiamond-based organosilica nanoparticles for two-photon imaging and antibacterial photodynamic therapy

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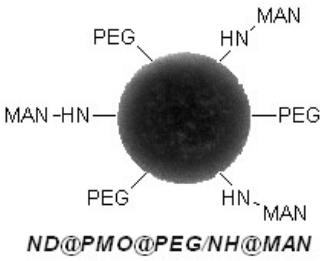
Nanodiamonds (NDs) with exceptional optical, thermal and mechanical properties emerged on the global scientific scene, especially in biomedicine and bioanalysis fields. Nanodiamond-based periodic mesoporous organosilica nanoparticles (ND@PMO NPs) recently displayed in vitro photosensitizing capability on MCF-7 breast cancer cells with two-photon excited photodynamic therapy (TPE-PDT) and fluorescence properties for two-photon imaging (TPI)[1-2]. With no silica source, these nanoparticles synthesized through sol-gel condensation in mild conditions were holding good biocompatibility due to their PMO-based shell.



ND@PMO@PEG/NH@MAN

In this work, we described ND@PMO NPs with various size distribution depending on the nature of hydroxylated NDs and organosilica precursor employed. NPs were further modified. First, amino-silane and PEG-silane were grafted, the last bringing antifouling properties and suspension stability. Then, a mannose squarate derivative (MAN) was anchored through the amino function to target bacterial infections by specific binding onto FimH lectins of bacteria membrane[3-4].

FTIR spectra displaying ND, PEG, MAN and siloxane network characteristic bands confirmed the structure, reinforced by surface zeta potential shift from very positive values (amino groups, > 20 mV) to negative values (mannose hydroxyl groups, < -20 mV). UV-vis absorption spectra regression allowed determining the MAN-grafting rate.

The long-term objective is to apply these carbohydrate-grafted NPs to antibacterial purpose, especially wound healing, by performing TPI and synergistic TPE-PDT and chemotherapy by the mean of vancomycin loading into PMO pores.

1. Bondon, N. et al.., Nanodiamonds for bioapplications, recent developments. *Journal of Materials Chemistry B* **2020,** *8* (48), 10878-10896.
2. Jimenez, C. M. et al., Nanodiamond–PMO for two-photon PDT and drug delivery. *Journal of Materials Chemistry B* **2016,** *4* (35), 5803-5808.
3. Brevet, D. et al., Mannose-targeted mesoporous silica nanoparticles for photodynamic therapy. *Chemical Communications* **2009,** (12), 1475.
4. Sperling, O. et al., Evaluation of the carbohydrate recognition domain of the bacterial adhesin FimH: design, synthesis and binding properties of mannoside ligands. *Organic & Biomolecular Chemistry* **2006,** *4* (21), 3913.

The 5th Photodynamic Day

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International Day of Light 16 May

Acetylated lignin nanoparticles as an universal formulation for photosensitizers

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Introduction. Lignin valorization is a topic that has started to attract attention from the scientific community, due to the easiness of lignin chemical tuning and due to its low cost of production. Lignin has appeared as an interesting material for biomedical applications, namely, as a drug carrier. Several examples have demonstrated that lignin nanoparticles are able to transport antineoplasic drugs,[1] pesticides,[2] and even photosensitizers.[3] Although it has been demonstrated the feasibility of encapsulation of 5,10,15,20-tetrakis (4-hydroxyphenyl)-21H,23H-porphine (**THPP**), the extensiveness of this result to other types of photosensitizers needs to be analyzed. **Methodology**. Four derivatives of **THPP** were prepared and encapsulated inside acetylated lignin nanoparticles. The nanoparticles were characterized through DLS, zeta potential, UV-vis absorption, fluorescence emission and singlet oxygen production. Furthermore, their stability on aqueous conditions and in several pH conditions was analyzed. Finally, nanoparticles were tested against planktonic cells of *Staphylococcus aureus* and *Escherichia coli*, as Gram-positive and Gram-negative models. **Results**. All the porphyrins were efficiently encapsulated. The porphyrins maintained their photophysical properties (i.e. UV-vis absorption profile, fluorescence, singlet oxygen production). Furthermore, the encapsulated porphyrins demonstrated stability over pH changes in the media and over storage, without evidence of leakage to the media. When tested against bacteria, they were able to efficiently photoeradicate Gram-positive bacteria, while Gram-negative bacteria was only successfully photoeradicated by cationic-porphyrin-loaded nanoparticles. **Conclusions.** Porphyrin encapsulation was achieved, regardless of the chemical structure of the porphyrins, resulting in a "universal" formulation for photosensitizers.[4] The obtained nanoparticles kept their photophysical features and lead to bacterial death of Gram-positive bacteria. Several examples in literature indicate that Gram-negative photoeradication can be enhanced by the presence of cationic charges. Nevertheless, from the two cationic-porphyrin loaded nanoparticles prepared, although both had a positive zeta potential, only one was able to eradicate *E. coli*. These results pave the way for better materials against Gram-negative bacteria proliferation.

References

(1)Figueiredo, P.; Lintinen, K.; Kiriazis, A.; Hynninen, V.; Liu, Z.; Bauleth-Ramos, T.; Rahikkala, A.; Correia, A.; Kohout, T.; Sarmento, B.; Yli-Kauhaluoma, J.; Hirvonen, J.; Ikkala, O.; Kostiainen, M. A.; Santos, H. A. *Biomaterials* **2017**, *121*, 97–108. https://doi.org/10.1016/j.biomaterials.2016.12.034.

(2) Zhou, M.; Wang, D.; Yang, D.; Qiu, X.; Li, Y. *Ind. Crops Prod.* **2019**, *137* (May), 453–459. https://doi.org/10.1016/j.indcrop.2019.04.037.

(3) Maldonado-Carmona, N.; Marchand, G.; Villandier, N.; Ouk, T.-S.; Pereira, M. M.; Calvete, M. J. F.; Calliste, C. A.; Żak, A.; Piksa, M.; Pawlik, K. J.; Matczyszyn, K.; Leroy-Lhez, S. *Front. Microbiol.* **2020**, *11*. https://doi.org/10.3389/fmicb.2020.606185.

(4) Maldonado-Carmona, N.; Ouk, T.; Villandier, N.; Calliste, C. A.; Calvete, M. J. F.; Pereira, M. M.; Leroy-Lhez, S. *Antibiotics* **2021**, *10* (5), 513. https://doi.org/10.3390/antibiotics10050513.

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Covalently cross-linked tetrafunctionalized *m*-THPC chitosan hydrogels as delivery platforms

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Photodynamic therapy (PDT) is an anti-cancer treatment method, which uses the combined effect of a photosensitizing drug, light, and oxygen to cause selective damage to target tissue.[1] The second generation photosensitizer (PS) 5,10,15,20-tetrakis(*m*-hydroxyphenyl)chlorin (*m*-THPC) is a widely characterized, clinically tested, and commercially available drug.[2] In order to develop advanced treatment modalities there is a need for improved drug delivery platforms. Hydrogels, which have been investigated as effective drug delivery systems, can prevent PSs aggregation due to their ability to swell in aqueous media.[3] Chitosan (CS), a natural polysaccharide, is a suitable biodegradable material for hydrogel formulation and has been used in pharmaceutical applications on account of its lack of toxicity and good biocompatibility.[4]

Herein, *m*-THPC was used as a starting point to obtain a library of compounds aimed at overcoming PS limitations while maintaining its photophysical and clinical properties. Substitution, esterification and Sonogashira coupling reactions were employed to modify the *m*-THPC skeleton providing aldehyde and carboxylic acid moieties used as a suitable synthetic handle for covalent cross-linking in the formation of CS hydrogels. Injectable, self-healing properties of hydrogels were confirmed by the rheological analysis. Tetrafunctionalized *m*-THPC derivatives, maintaining efficient singlet oxygen generation are under ongoing *in vitro* evaluation against melanoma cancer cells (B16F10). Prepared hydrogel formulations are expected to allow for a local, injectable administration towards melanoma tumors, while preventing from systemic side effects related to the *m*-THPC treatment.

References

1. T. J. Dougherty, C. J. Gomer, B. W. Henderson, G. Jori, D. Kessel, M. Korbelik, J. Moan, Q. Peng, *J. Nat. Cancer Inst.* **1998**, *90*, 889–905.
2. M. O. Senge, J. C. Brandt, *Photochem. Photobiol.* **2011**, *87*, 1240–1296.
3. B. Khurana, P. Gierlich, A. Meindl, L. C. Gomes-da-Silva, M. O. Senge, *Photochem. Photobiol. Sci.* **2019**, *18*, 2613–2656; b) S. Belali, H. Savoi, J. M. O'Brien, A. A. Cafolla, B. O'Connell, A. R. Karimi, R. W. Boyle, M. O. Senge, *Biomacromolecules* **2018**, *19*, 1592–1601.
4. M. Dash, F. Chiellini, R. M. Ottenbrite, E. Chiellini, *Prog. Polym. Sci.* **2011**, *36*, 981–1014.

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Photoactivatable metabolic warheads enable precise and safe ablation of target cells in vivo

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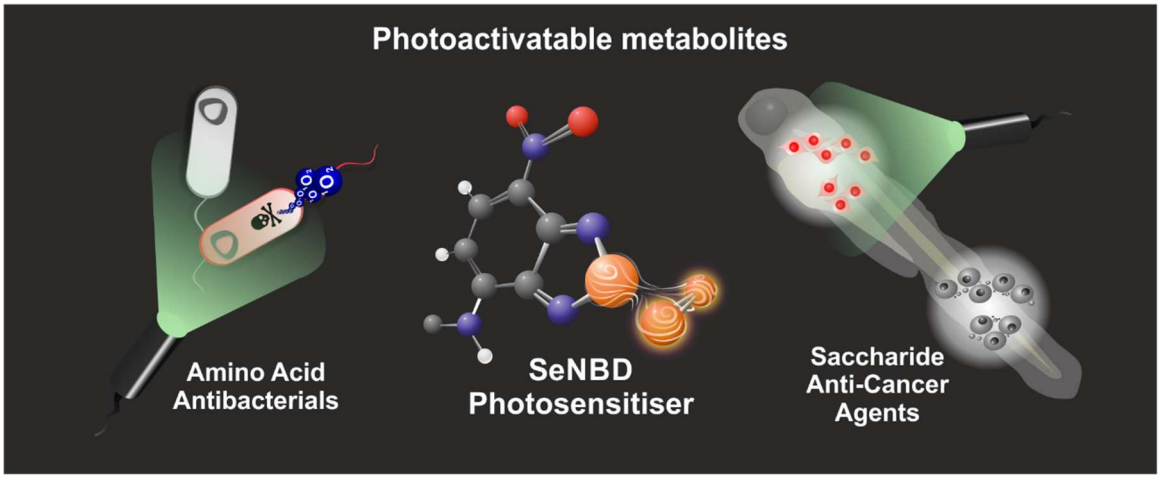
Photoactivatable molecules enable ablation of malignant cells under the control of light, yet current agents can be ineffective at early stages of disease when target cells are similar to healthy surrounding tissues. We have created a chemical platform based on amino substituted benzoselenadiazoles to build photoactivatable probes that mimic native metabolites as indicators of disease onset and progression. Through a series of synthetic derivatives, we have identified the key chemical groups in the benzoselenadiazole scaffold responsible for its photodynamic activity, and subsequently designed photosensitive metabolic warheads to target cells associated with various diseases, including bacterial infections and cancer. We demonstrate that versatile benzoselenadiazole metabolites can selectively kill pathogenic cells but not healthy cells with high precision after exposure to non-toxic visible light, reducing any potential side effects in vivo. This chemical platform provides powerful tools to exploit cellular metabolic signatures for safer therapeutic and surgical approaches.[1]



References

(1) Benson, S.; de Moliner, F.; Fernandez, A.; Kuru, E.; Asiimwe, N. L.; Lee, J.-S.; Hamilton, L.; Sieger, D.; Bravo, I. R.; Elliot, A. M.; Feng, Y.; Vendrell, M. Photoactivatable Metabolic Warheads Enable Precise and Safe Ablation of Target Cells in Vivo. *Nat. Commun.* **2021**, *12*, 2369. https://doi.org/10.1038/s41467-021-22578-2.

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Metalloporphyrin-based nanoarchitectures for wireless intracellular communication

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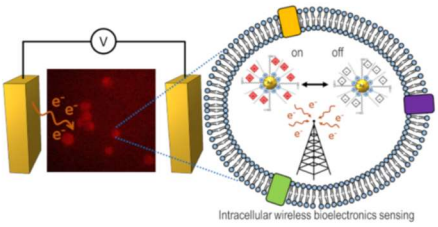
The development of "wireless" electronic systems to both sense and actuate cell behaviour is an urgent requirement in the field of bioelectronics medicine to make an impact on healthcare.[1] Recently we reported the first example of an innovative intracellular wireless electronic communication system on the nanoscale at the surface of conductive nanoparticles at unreported low potentials.[2] The system is made functional by modifying water-soluble gold nanoparticles (ws-AuNPs) incorporating a Zn(II) meso-tetrakis(4-carboxyphenyl)porphyrin sodium salt (Na-ZnTCPP), which are taken up by cells and are shown to be biocompatible. It is demonstrated that the fluorescence can be modulated depending on the redox state of the Zn-porphyrin modified gold nanoparticles when applying an external electrical field. This provides an attractive new "wireless" approach to develop novel bioelectronic devices for modulating and sensing cellular behaviour using intracellular monitoring.



References

1. P. Sanjuan-Alberte, F. J. Rawson, *Ther. Delivery*, **2019**, *10*, 139−142.
2. P. Sanjuan-Alberte, A. Jain, A. J. Shaw, S. A. Abayzeed, R. Fuentes Domínguez, M. E. Alea-Reyes, M. Clark, M. R. Alexander, R. J. M. Hague, L. Pérez-García, F. J. Rawson, *ACS Appl. Nano Mater.*, **2019**, *2*, 6397−6408.

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Porphyrinoids bearing pyrazole-pyridinium units as photosensitizers for photoinactivation of planktonic and biofilm forms of *Escherichia coli*

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Bacteria in their planktonic or biofilm forms can cause severe and chronic infections in humans with high tolerance to the conventional treatments.[1,2] Antimicrobial photodynamic therapy (aPDT) can be an efficient therapeutic alternative to inactivate microorganisms by the combination of a photosensitizer molecule (PS), dioxygen and visible light to induce the formation of reactive oxygen species (ROS) that leads to cell death.[3,4] For this purpose, cationic Pors and Chls (**1a** and **2a**) bearing pyrazol-pyridinium groups were synthesized and characterized, and their aPDT efficiency against planktonic and biofilm forms of *E. coli* was investigated.

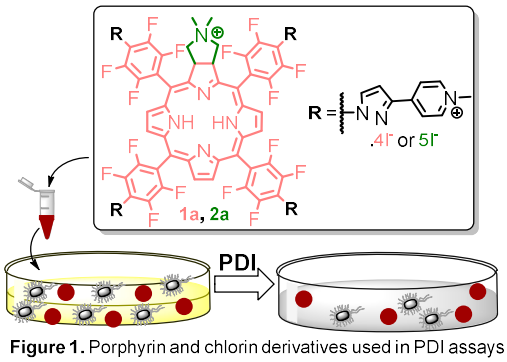

Figure 1. Porphyrin and chlorin derivatives used in PDI assays

References

1.a) Lourenço, L. M. O.; Rocha, D. M. G. C.; Ramos, C. I. V.; Gomes, M. C.; Almeida, A.; Faustino, M. A. F.; Almeida Paz, F. A.; Neves, M. G. P. M. S.; Cunha, Â.; Tomé, J. P. C. Photoinactivation of planktonic and biofilm forms of *Escherichia coli* through the action of cationic zinc(II) phthalocyanines. *ChemPhotoChem* **2019**, 3, 251–260; b) Vieira, C.; Santos, A.; Mesquita, M. Q.; Gomes, A. T. P. C.; Neves, M. G. P. M. S.; Faustino, M. A. F.; Almeida, A. Advances in aPDT based on the combination of a porphyrinic formulation with potassium iodide: Effectiveness on bacteria and fungi planktonic/biofilm forms and viruses. *J. Porphyr. Phthalocyanines* **2019**, *23*, 534–545.

2.a) Calmeiro, J. M. D.; Gamelas, S. R. D.; Gomes, A. T. P. C.; Faustino, M. A. F.; Neves, M. G. P. M. S.; Almeida, A.; Tomé, J. P. C.; Lourenço, L. M. O. Versatile thiopyridyl/pyridinone porphyrins combined with potassium iodide and thiopyridinium/methoxypyridinium porphyrins on *E. coli* photoinactivation. *Dyes. Pigments*. **2020**, 181, 108476; b) Calmeiro, J. M. D.; Dias, C. J.; Ramos, C. I. V.; Almeida, A.; Tomé, J. P. C.; Faustino, M. A. F.; Lourenço, L. M. O. Comparative photodynamic inactivation of bioluminescent *E. coli* by pyridinium and inverted pyridinium chlorins. *Dyes. Pigments.* **2020**, 173, 107410.

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Effect of malachite green-mediated photodynamic therapy on *Leishmania tropica* promastigotes.

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Leishmaniasis is a common protozoon disease caused various clinical forms, from deadly internal organ involment to self-healing skin lesion and it is transmitted by a vector called Phlebotomus (David and Craft, 2009; WHO 2010). *Leishmania* species have been the primary target for photodynamic therapy (PDT). Malachite green is a cationic dye used for staining which is obtained from benzaldehyde and dimethyl aniline and has a triphenylmethane structure. Triarylmethane family could be used as a potential photosensitizer since it induces degradation of the cell membrane potential (Kowaltowski,1999). The purpose of this study was to determine the effect of malachite green-mediated PDT in *Leishmania tropica* promastigotes. The photodynamic activity of malachite green on the cell viability, morphological changes and apoptosis of *Leishmania tropica* was investigated by XTT,giemsa staining and flow cytometry and scanning electron microscopy, respectively. Morphological evaluation of promastigotes after photodynamic treatment indicated a loss of cytoplasmic material and observed wide, spherical shapes and ghost cells in promastigotes. Scanning electron microscopy showed a decrease in cell size, loss of flagella, acquisition of ovoid and irregular shape and severe distortion in cell membrane. Malachite green mediated PDT groups exhibited an intense red fluorescence signal. In samples treated with malachite green mediated PDT, a depolarization of the mitochondrial membrane potential was observed. At 26 °C, there was a dose-dependent increase in apoptosis, cell cycle arrest, Mitchondria membrane potential and ROS generation in *L. tropica* promastigotes indicating that 1 hour incubations of MG followed by 30 minutes of PDT induced cell death. As a result, we determined that increases in apoptosis and ROS were caused by PDT+ malachite green and not associated solely with malachite green. Therefore, the results indicated that PDT associated with malachite green represents a promising alternative to cutaneous leishmaniasis treatment.

References

1. David, C.V., Craft, N. Cutaneous and mucocutaneous leishmaniasis. Dermatol Ther 2009, 22,491-502.
2. Meeting of the WHO expert committee on the control of leishmaniases, WHO Technical Reports Series 949, Geneva: WHO, March (2010).
3. Kowaltowski, A.J., Turin, J., Indig G.L, Vercesi, A.E. Mitochondrial effects of triarylmethane dyes. J. Bioenerg. Biomemb.1999, 31, 581-590.

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Singlet oxygen enhancement through encapsulation of a sulfonated zinc phthalocyanine within a supramolecular gel

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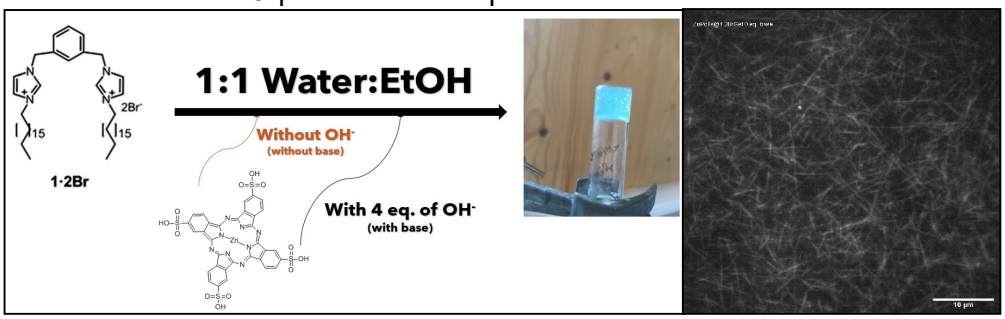
Nanostructured materials[1] are extensively studied because their novel properties enable challenging applications in all fields of science. However, the exact influence of their supramolecular structure on their properties remains poorly understood. We have prepared and characterized nanostructured materials such as bio-functionalized silicon microparticles[2a], inorganic and metallic nanoparticles[2b] and supramolecular hydrogels[2c,d] designed for biological applications as sensing and delivering to living cells, with particular attention to their potential use in photodynamic therapy. One of our more recent findings arises from the incorporation of a zinc(II) phthalocyanine photosensitizer (PS) into a supramolecular hydrogel (Figure), showing that the supramolecular organization improves the SO generation with respect to solutions of the parent PS. Furthermore, the addition of NaOH base during gel preparation has shown to influence the photophysical characteristics along with the fibrillar structure at the microscale as revealed by SEM and TIRF microscopy. The enhancement in SO generation induced by this type of hybrid material makes it an attractive candidate to be used in different applications when efficient SO production is required.



REFERENCES

1. J. Jeevanandam, A. Barhoum, Y. S. Chan, A. Dufresne, M. K. Danquah. *Beilstein J. Nanotechnol.*, **2018**, *9*, 1050–1074.
2. a) N. Torras, J. P. Agusil, P. Vázquez, M. Duch, A. M. Hernández-Pinto, J. Samitier, E. J. de la Rosa, J. Esteve, T. Suárez, L. Pérez-García, J. A. Plaza. *Adv. Mater.*, **2016**, *28*, 1449–1454. b) M. E. Alea-Reyes, O. Penon, P. García Calavia, M. J. Marín, D. A. Russell, L. Pérez-García. *J. Colloid Interface Sci.*, **2018**, *521*, 81 – 90. c) G. Bruce, M. Samperi, D. B. Amabilino, M. Duch, J. A. Plaza L. Pérez-García. *J. Porphyr. Phthalocyanines*, **2019**, *23*, 223–233. d) M. Samperi, D. Limón, D. B. Amabilino, and Lluïsa Pérez-García, *Cell Rep. Phys. Sci.*, **2020**, *3*, 100030.

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5-AMINOLEVULINIC ACID-MEDIATED PHOTODYNAMIC DIAGNOSIS IN COLON CANCER

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Introduction: Photodynamic diagnosis (PDD) is a technique currently under clinical assessment for visualization and local destruction of malignant tumors and premalignant lesions. This technique is used to diagnose cancer such as basal cell carcinoma, bladder cancer, brain cancer, cervical cancer, breast cancer. In this method, small changes in the tissue can be detected using a white light endoscopy procedure with a special photosensitizer. 5-Aminolevulinic acid (5-ALA) is a naturally occurring amino acid derivative that acts as an endogenous substrate and precursor to protoporphyrin IX (PpIX). PpIX is a heme precursor in the biosynthetic pathway that emits a strong red fluorescence upon excitation with blue light[1,3]. Since 5-ALA is analogous to amino acids, it is rapidly absorbed after ingestion and immediately metabolized to heme in normal cells. In various cancer cells, exogenous administration of excessive amounts of 5-ALA increases the cellular level of PpIX, resulting in a higher accumulation of PpIX in cancer cells than in normal cells[2,3].
In this study, we aimed to determine the conditions required for the most effective photodynamic recognition of the fluorescence produced by 5-ALA stimulated PpIX in colon cancer in vitro.

Keywords: Photodynamic diagnosis, 5-Aminolevulinic acid, In Vitro, Fluorescence Intensity

Material and Method: Human colorectal carcinoma (HT-29) cells were cultured in RPMI medium supplemented with 10% fetal bovine serum and 1% antibiotics at 37°C in 5% CO2. Cells were seeded in plastic 35 mm plates (3×10^5 cells per well), cultured for 48 h and then washed twice with PBS. Afterward, cells were treated with different concentrations of 5-ALA: 100 µg/ml, 200 µg/ml, 300 µg/ml, 500 µg/ml, 1000 µg/ml, 1500 µg/ml in medium alone (control). The cells were incubated in the dark at 37°C in 5% CO2 for 3 hours[3].

Cell images were taken using a ZEISS Axio Vert.A1 Inverted Microscope equipped with an Axiocam 208. We used x10 magnification. Pictures of randomly selected fields were taken twice in the same place: a) Bright-field image for detection of the area covered by cells; b) Fluorescence image using 352–402 nm bandpass filters for excitation light and lowpass for more than 410 nm for cell images[4]. After taken images, to measure the fluorescence intensity of PpIX we used the Image J method[5].

The viability of 5-ALA-treated cells was determined after 24 h by the application of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) (Sigma-Aldrich, Steinheim, Germany).

Results: After 24 hours 5-ALA treated, cell viability was measured by MTT. 5-ALA applications showed different effects on cell viability. Among control, 100 µg/ml, 200 µg/ml, and 300 µg/ml 5-ALA concentrations didn't produce a statistically significant change in cell viability, while a significant decrease at 1000 µg/ml 5-ALA compared with 500 µg/ml 5-ALA was recorded (p<,0001).

To determine the levels of PpIX accumulation in living single cells of HT-29 cells, we first treated HT-29 cells with 5-ALA and analyzed the fluorescence intensity of PpIX by the image J method. According to the results of fluorescence intensity, the highest fluorescence intensity was at 1500 µg/ml 5-ALA. We noticed that there was a significant increase in fluorescence intensity between each 5-ALA concentration (p<,0001).

Conclusion: We demonstrated that although the highest fluorescence intensity was at 1500 µg/ml 5-ALA, it is also the concentration with the lowest cell viability. It was observed the 5-ALA concentrations increase in parallel with the fluorescence intensity. In conclusion, it was determined that the optimum 5-ALA concentration was 500 µg/ml, and the optimum incubation time required for observable fluorescence for ALA-stimulated PpIX was 3 hours.

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References

(1) Nemes, A.; Fortmann, T.; Poeschke, S.; Greve, B.; Prevedello, D. 5-ALA Fluorescence in Native Pituitary Adenoma Cell Lines: Resection Control and Basis for Photodynamic Therapy (PDT), Plos One, 2016.

(2) Rosin, F.C.P.; Teixeira, M.G.; Pelissari, C.; Corrêa, L. Resistance of oral cancer cells to 5-ALA-mediated photodynamic therapy. J Cell Biochem 2018, 119:3554–62.

(3) Fernandez, J.M.; Bilgin M.D.; Grossweiner, L.I. Singlet Oxygen Generation by Photodynamic Agents, J. Photochem. Photobiol. B: Biol., 1997, 37: 131-140.

(4) Ramonaitea, R.; Petrolisa, R.; Unay S.; Kiudelis, G.; Skieceviciene, J.; Kupcinskas, L.; Bilgin M.D.; Krisciukaitis, A. Mathematical morphology-based imaging of gastrointestinal cancer cell motility and 5-aminolevulinic acid-induced fluorescence, Biomed. Eng.-Biomed. Tech. 2019

(5) Fitzpatrick, M. Measuring cell fluorescence using ImageJ, Available at http://theolb.readthedocs.io/en/latest/imaging/measuring-cell-fluorescence-usingimagej.html#measuring-cell-fluorescence-using-imagej, August 4. 2017.

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Photophysical properties of a N^C^N-coordinated Pt(II) complex: effect of DNA binding and intercalation

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Cyclometalated platinum(II) complexes containing tridentate π-conjugated organic ligands have been receiving an increase of interest as they display rich and diverse photoluminescent properties that are sensitively affected by the local environment[1].
These complexes can exert their cytotoxic action via classical mode of action, aquation and subsequently covalent binding to the DNA base pairs or by reversible interactions such as intercalation. In fact, the planar motif of the ligand can render the complex able to establish non-covalent π- π interactions.
The investigation of the antiproliferative properties of this kind of complexes has demonstrated that they are promising photosensitizers under visible light, capable to produce singlet oxygen[2].
The photophysical properties of the complex Pt(N^C^N)Cl, where the N^C^N ligand is 2,6-dipyrido-4-methyl-benzenechloride, are investigated in detail by means of DFT and its TD-DFT time-dependent extension together with Molecular Dynamics simulations. The suitability of the investigated complex to act as a photosensitizer has been verified calculating spectroscopic properties for both the unperturbed complex and its aquated and guanine bound forms.
Using Molecular Dynamics simulation outcomes as starting point, the photophysical properties of both the DNA intercalated complex and the complex bound to DNA have been evaluated aiming at establishing how such interactions can affect the activity of the complex under examination.

References

1. Doherty, R. E.; Sazanovich, I. V.; McKenzie, L. K.; Stasheuski, A. S.; Coyle, R.; Baggaley, E.; Bottomley, S.; Weinstein, J. A.; Bryant, H. E. Photodynamic Killing of Cancer Cells by a Platinum(II) Complex with Cyclometallating Ligand. *Sci Rep* **2016**, *6* (1), 22668.
2. Williams, J. A. G.; Beeby, A.; Davies, E. S.; Weinstein, J. A.; Wilson, C. An Alternative Route to Highly Luminescent Platinum(II) Complexes: Cyclometalation with NΛCΛN-Coordinating Dipyridylbenzene Ligands. *Inorg. Chem.* **2003**, *42*, 8609-8611.

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Light Harvesting Bodipy Dangled Pt(II) Schiff Base Complex: Singlet/Triplet Energy Transfer and Application in Triplet-triplet Annihilation Upconversion

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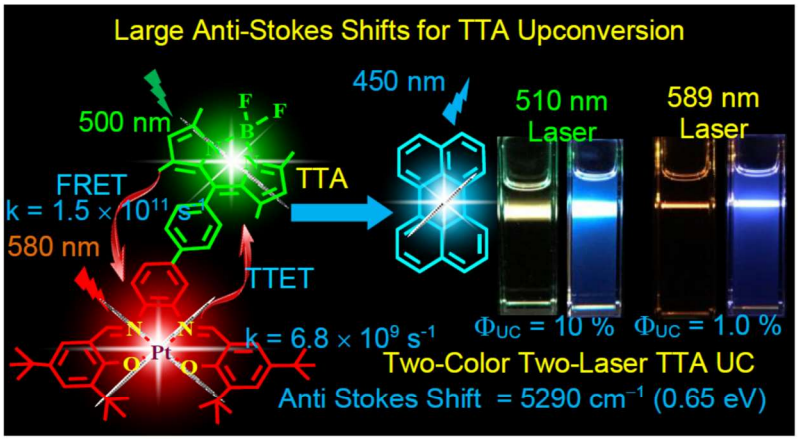
Abstract: Bodipy dangled Pt(II) complex (**Pt–BDP**) dyad has been synthesized and the detailed photophysical properties were investigated. **Pt–BDP** containing two different chromophores constitute singlet/triplet energy donor/acceptor pair, were confirmed by the transient absorption spectroscopy (k_{FRET} = 1.5 × 10^{11} s^{-1}, 6.7 ps) followed by an intersystem crossing (< 0.5s) and the triplet state lifetime (τ_T) is 103.2 µs. Conversely, the reference complex **Pt–Ph** shows an intersystem crossing (< 0.5s), and τ_T = 3.48 µs. **Pt–BDP** was used as triplet photosensitizer for triplet–triplet annihilation (TTA) upconversion (k_{TTET} = 6.8 × 10^9 s^{-1}). With selective excitation into the Pt(II) coordination center at lower energy, and by intramolecular triplet–triplet–energy–transfer (TTET) to Bodipy to form the long–lived Bodipy–localized triplet state, the anti–Stokes shift of the upconversion is increased from 5290 cm^{-1} (0.65 eV) than the direct excitation of the Bodipy moiety (2660 cm^{-1}, 0.33 eV) with high upconversion quantum yields (Φ_{UC} = 10.0 and 2.0 %).



References
1. Chen, K.; Hussain, M.; Razi, S. S.; Hou, Y.; Yildiz, E. A.; Zhao, J.; Yaglioglu, H. G.; Donato, M. D.; *Inorg. Chem.*, **2020**, *59*, 14731–14745.
2. Razi, S. S.; Koo, Y. H.; Kim, W.; Yang, W.; Wang, Z.; Gobeze, H.; D'Souza, F.; Zhao, J.; Kim, D.; *Inorg. Chem.*, **2018**, *57*, 4877–4890.
3. Wang, Z.; Zhao, J.; *Org. Lett.*, **2017**, *19*, 4492–4495.
4. Wang, Z.; Zhao, J.; Barbon, A.; Toffoletti, A.; Liu, Y.; An, Y.; Xu, L.; Karatay, A.; Yaglioglu, H. G.; Yildiz, E. A.; Hayvali, M.; *J. Am. Chem. Soc.*, **2017**, *139*, 7831–7842.

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Increase in singlet oxygen production of a photosensitizer transported in unilamellar vesicles due to due to the addition of magnetite nanoparticles

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The biocompatible nature of L-α phosphatidylcholine (LUV) unilamellar vesicles makes them a vehicle of interest for photosensitive molecules that are efficient in generating singlet oxygen but soluble in toxic organic solvents.

Due to its contrast properties, the incorporation of magnetite superparamagnetic nanoparticles (M) during the generation of the lipid film generates a system (MLUV) with the potential to achieve a defined location in the target site. It is in this context we studied the vehiculization of the molecule 2, 3,9,10,16,17,23,24 octakis [(N,N dimethyalmino) ethysulfanyl)] phthalocyaninatozinc (II) (Pc) in nanoparticles (MLUVPC), as well as the effect that the composition of the nanoparticulate system generates in the photophysical properties of the photosensitive molecule; in particular on the quantum yield on single oxygen. The characterization of MLUV and MLUVPc by means of TEM images showed a particle size distribution of 130 nm. The presence of superparamagnetic magnetite is verified by hysteresis curves (SQUID). Finally, it was observed that the ΦΔ of Pc in LUV (0,51) decreases with respect to that of THF (0,69) although it experiences a significant increase in MLUVPc (0,72) compared to previous systems. This increased quantum yield of singlet oxygen from Pc in MLUVPc occurs/may occur because the built-in magnetite exerts a heavy atom effect. The heavy atom produces an increase in the quantum yield of the triplet, that being an alternative way to fluorescence to deactive the excited state of the photosensitizer. It is manifested as a decrease in the fluorescence quantum yield (Φf) (0,05) in MLUV with respect to the value in LUV (0,10) and in THF (0,26). İn this way, the action of the nanoparticulate magnetite as a heavy atom is verified by the increase in ΦΔ and the decrease in Φf of Pc in MLUV with respect to Pc in LUV.

References

Diz et al., 2016. *Journal of Photochemistry and Photobiology A: Chemistry* 316 (2016) 44-51

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Synthesis and spectral properties of gem-dimethyl chlorin photosensitizers

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Photodynamic therapy (PDT) is a developing non-invasive targeted therapy which involves systemic or topical administration of a photosensitizer (PS), which after irradiation of a specific wavelength of light reacts with the coexisting molecular oxygen. As a result, highly reactive singlet oxygen ($^1O_2$) and other reactive oxygen species (ROS) can be formed leading to specific apoptotic or necrotic cell death of the cancer cells.[1]

In this study we aim to develop novel non-toxic PSs, *i.e.*, chlorins which bear a *gem*-dimethyl group, attributing to their resistance to oxidation. These compounds have potential use as anticancer or antimicrobial agents and their photophysical properties are described herein.

Synthesis was performed following a method reported by Lindsey and co-workers.[2] A complete characterization of their spectral and photophysical properties (Φ_f, Φ_{isc}, Φ_{ic}, Φ_Δ, τ_S, τ_T, k_f, k_{ic}, k_{isc}, k_q) is accompanied by density functional calculations (DFT) and time dependent (TD) DFT to investigate the features of the frontier molecular orbitals. The metallochlorins exhibit high triplet state yields (Φ_{isc} = 0.80 – 0.90) and excellent singlet oxygen quantum yields in methanol and ethanol (Φ_Δ = 0.60 – 0.85) and the free base analogues exhibited suitable triplet state yields (Φ_{isc} = 0.70 – 0.80) and singlet oxygen quantum yields (Φ_Δ = 0.40 – 0.70). Results show that the chlorins can be potential PS candidates for PDT, given that they display high singlet oxygen quantum yields in polar solvents, modest fluorescence quantum yields (Φ_f = 0.03 – 0.14) and moderate triplet state lifetimes (τ_T = 150 – 220 ns) upon photoexcitation.[3]

Future work includes the optimization of the photophysical properties of the chlorins (red-shifted absorption, high triplet state yields, long triplet lifetimes and high singlet oxygen quantum yields) and enhancing the water solubility through modification of the periphery with a variety of substituents. Additionally, *in vitro* evaluation will be employed in future.

References

1. Wiehe, A.; O'Brien, J. M; Senge, M.O. Trends and targets in antiviral phototherapy. *Photochem. Photobiol. Sci.* **2019**, *18* (11), 2565-2612.
2. Ptaszek, M.; McDowell, B. E.; Taniguchi, M.; Kim, H. J.; Lindsey, J. S. Sparsely substituted chlorins as core constructs in chlorophyll analogue chemistry. Part 1: Synthesis. *Tetrahedron*, **2007**, *63* (18), 3826-3839.
3. Melissari, Z.; Sample, H. C.; Twamley, B.; Williams, R. M.; Senge, M. O. Synthesis and spectral properties of gem-dimethyl chlorin photosensitizers. *ChemPhotoChem*, **2020**, *4* (8), 601-611.