Pharma | Technology Offer

Novel Nanoparticulate Photosensitizers for Daylight-driven Activation

Field of application

Photocatalysts are highly relevant for a wide range of applications, such as selective oxidation (e.g. in organic synthesis), photocatalytic degradation of organic molecules and germs (e.g. for water purification), or photodynamic therapy (e.g. for tumor therapy). Especially, daylight-activated photocatalysts are highly promising due to the ubiquitious availability of daylight and its less harmful interaction with tissue.

Here, we present two concepts and novel types of nanomaterials as efficient daylight-activated photocatalysts that are activated by blue, green, and even red light. The photocatalysts exhibit high photostability and excellent uptake into cells. Whereas they show high phototoxicity the systemic toxicity is low. Aiming at medicine, specific interest can be related not only to the treatment of near-surface tumors but also to inter- or post-surgery killing of individual cancer cells remaining after extraction of the solid primary tumor.

State of the art

In general, two classes of photosensitizers are widely discussed: molecular photosensitizers (most often porphyrine-based), and inorganic nanoparticles, including various metal oxides (*e.g.* TiO_2, ZnO, $BiVO_4$, Ag_3PO_4). Molecular photosensitizers are also often encapsulated in an inorganic matrix (*e.g.* SiO_2, Fe_2O_3). These types of photosensitizers exhibit specific disadvantages, such as the presence of harmful and/or expensive metals, low photostability, limited cell uptake, high systemic toxicity, heavy agglomeration under physiological conditions due to strong hydrophobic interaction (*e.g.* porphyrins) or low colloidal stability (*e.g.* nanoparticles). Inorganic oxide nanoparticles often suffer from UV-light activation, having a limited penetration depth and being harmful to cells and tissue.

All in a nutshell, there is still a strong need for agents with further optimized photophysical characteristics and depth of light penetration.

Innovation

At the Karlsruher Institut für Technologie (KIT) novel inorganic-organic hybrid nanoparticles (IOH-NPs) such as $La_4^{3+}[TPPS_4]_3^{4-}$ and $Gd_4^{3+}[AlPCS_4]_3^{4-}$ ($AlPCS_4$: aluminium(III) chlorido phthalocyanine tetrasulfonate; $TPPS_4$: tetraphenylporphine sulfonate) as well as inorganic nanoparticles such as β-$SnWO_4$ and β-$SnMoO_4$ were developed.

They can be activated by blue to green and even red light. Both systems were also successfully tested *in vitro* (e.g. HepG2, HeLa cells) and *in vivo* (e.g. mice, zebrafish). $Gd_4^{3+}[AlPCS_4]_3^{4-}$ (in suspension) significantly outperforms the clinically approved H_4AlPCS_4 (in solution) in terms of photostability, $^1O_2$ generation, phototoxic effect in cells as well as suppression of microcapillary networks and vascular cord formation.

Due to the fluorescence of $AlPCS_4$ and the magnetism of Gd^{3+}, $Gd_4^{3+}[AlPCS_4]_3^{4-}$ is suitable for multimodal imaging, including optical imaging/OI and magnetic resonance imaging/MRI.

β-$SnWO_4$ and β-$MoWO_4$ are especially characterized by excellent phtostability. In contrast to the IOH-NPs, β-$SnWO_4$ and β-$MoWO_4$ are activated by blue light, which means a smaller penetration depth into the tissue.

Your benefits at a glance for β-$SnWO_4$ and β-$MoWO_4$

- ✓ Activated by blue light
- ✓ High chemical stability
- ✓ Excellent photostability

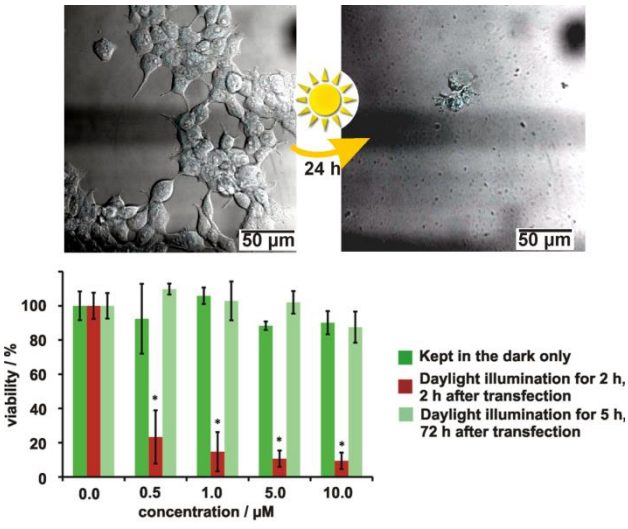

Figure 1: Phototoxic effect of ß-SnWO4 nanoparticles: Photos of HepG2 cells before and after exposure to daylight (top), MTT assays with HepG2 cells after cultivation with nanoparticles with storage in darkness, acute Phototoxicity after 2 h and low long-term toxicity after 72 h.

Your benefits at a glance for IOH-NPs

- ✓ Strong $^1O_2$ production upon green or red-light irradiation with quantum yields similar to the conventional molecules in solution
- ✓ Content of photocatalytic active porphyrins/phthalocyanine >80%
- ✓ $Gd_4^{3+}[AlPCS_4]_3^{4-}$ with $LD_{50} < 5x10^{-6}$ M
- ✓ Excellent cell membrane permeability
- ✓ High biocompatibility
- ✓ Low systemic toxicity
- ✓ Lower threshold for approval
- ✓ No inhibition of endothelial cell alignment and cord formation in darkness
- ✓ Multimodal imaging possible
- ✓ Simple, straightforward aqueous synthesis of the IOH-NPs

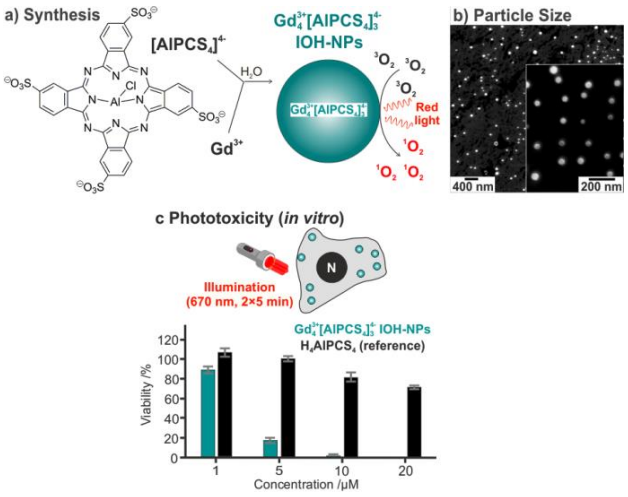

Figure 2: Schematic illustration of $Gd_4^{3+}[AlPCS_4]_3^{4-}$ IOH-NPs with photochemical $^1O_2$ production and phototoxicity under red-light illumination of the nanoparticles (green bars) in comparision to the clinically approved H_4AlPCS_4 (black bars).

Additional information

1) Saline Hybrid Nanoparticles with Phthalocyanine and Tetraphenylporphine Anions Showing Efficient Singlet-Oxygen Production and Photocatalysis; *Chem. Commun.* 2018, *54*, 1245–1248.

2) $Gd_4^{3+}[AlPCS_4]_3^{4-}$ Nanoagent Generating $^1O_2$ for Photodynamic Therapy; Adv. Funct. Mater. 2018, doi.org/10.1002/adfm.201801074.

3) Tin Tungstate Nanoparticles: A Photosensitizer for Photodynamic Tumor Therapy.
ACS Nano. 2016 Mar 22; 10(3):3149-57. doi: 10.1021/acsnano.5b03060. Epub 2016 Feb 25

4) In-vitro Fluorescence and Phototoxicity of ß-SnWO4 Nanoparticles
Chem. Commun. 2014, 50, 6600–6603.

Technology transfer

TLB GmbH manages inventions until they are marketable and offers companies opportunities for license and collaboration agreements.

Patent portfolio

4 patent families incl. several issued patents and pending patent applications:
WO2009/100800; WO2012/031645; WO2012/116784 & WO2015/144282.

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