New anticancer agents for photodynamic therapy

The challenge

Photodynamic therapy (PDT) is a technique commonly used to treat different types of cancers, especially skin cancers, and other diseases associated to the skin. This technique is based on the administration of a photosensitizer agent (PS) that, in the presence of oxygen and when exposed to light of the appropriate wavelength, is excited and produces highly cytotoxic reactive oxygen species (ROS) that destroy cancer cells. Currently, the most widely used PSs are based on organic fluorophores, which exhibit several drawbacks, including a lack of activity under hypoxic conditions and auto-degradation due to photobleaching. With the aim of developing an optimal PS for combating cancer more efficiently with PDT, researchers from the University of Barcelona are currently working on the development of novel PSs with operability within the phototherapeutic window (650-800nm) and under hypoxic conditions with the aim of treating deep-seated hypoxic tumors.

Technology

The researchers have developed a new family of PSs that can be efficiently photoactivated with far-red and NIR light. This radiation is non-toxic and penetrates deeper into human tissues than blue or green light. In addition, the PSs are highly photostable, cell permeable and have a clear subcellular target (mitochondria), which makes them promising candidates for clinical use. So far, several PS candidates have been synthesized and biologically evaluated in a panel of cancer cell lines under visible and NIR light. It is important to note that the compounds remain highly phototoxic under hypoxia conditions, which would allow to expand the potential applications of PDT for treating deep-seated hypoxic tumors. In addition, the PSs developed so far can be functionalized with other accessory molecules such as targeting ligands to deliver them selectively to cancer cells or even with other antitumoral agents that could be photoreleased when the PSs are exposed to light.

Results of photocytotoxicity studies under normoxia on 2D cell monolayers (CT-26) using PpIX as a positive control.

	PpIX		Lead 1		Lead 2	
	IC_{50} (nM)	PI[a]	IC_{50} (nM)	PI[a]	IC_{50} (nM)	PI[a]
Dark	>100000	-	>250000	-	>250000	-
540nm	320 ± 90	>312	8.2 ± 0.6	>30487	25 ± 2	>10000
595nm	400 ± 10	>250	13 ± 3	>19230	25 ± 4	>10000
620nm	660 ± 210	>151	42 ± 6	>5052	17 ± 3	>14705
645nm	170 ± 210	>588	48 ± 3	>5208	7.4 ± 0.6	>33783
670nm	770 ± 200	>129	1460 ± 450	>171	36 ± 3	>6944
740nm	2100 ± 200	>50	31300 ± 6100	>8	760 ± 60	>329

Phototoxic index (PI) = IC_{50} (dark-non-irradiated cells)/IC_{50} (irradiated cells).

Stage of development

Cyto- and phototoxicity of the two most promising lead compounds have been tested in *in vitro* assays in a mouse colon carcinoma cell line (CT-26). Both compounds showed no activity in the dark (not toxic) but became highly phototoxic when irradiated at different wavelengths within the phototherapeutic window, even with highly penetrating far-red (645-670 nm) and NIR (740 nm) light. The tests have been performed using Protoporphyrin IX (PpIX) as a control, and the results show that both compounds outperform PpIX (one of the most clinically used PS). Moreover, one of the lead compounds has been tested in several human cancer (colon, lung, ovarian), leading to excellent phototoxicity activities after irradiation with a 740 nm laser. Very importantly, the compounds retain a good photoactivity under low oxygen conditions (2% O_2) which would facilitate the treatment of deep-seated hypoxic tumors.

Benefits

These new compounds provide many benefits and advantages:

- **High photostability**.
- **Non toxic in the dark**.
- **Highly cytotoxic** upon irradiation at wavelengths within the **phototherapeutic window** (650-800nm).
- **Good nanomolar activity** and **outstanding PI** values.
- **High phototoxicity under hypoxia conditions**.
- **Easier to synthesize** than conventional PS.
- **Functionalization** possibilities.

Lead compound 2 exhibits IC_{50} values in the very low nM range and impressive PI values (PI > 33783) after red light irradiation. Very importantly, this new PS agent displayed a good phototoxicity profile with highly penetrating NIR light (740 nm) and retained a good photoactivity under hypoxia (PI >3290).

Represented Institutions and inventor:

The researchers behind the innovation belong to the "Bioimaging, Bioconjugation, Structural Studies and Therapeutic Applications Involving Small Molecules, Peptides and Oligonucleotides" research group at the University of Barcelona. The research group aims to develop new chemical tools for bioimaging and therapeutic applications based on low molecular weight compounds and biomolecules. The Principal Investigator behind this line of research is Dr. Vicente Marchán, who also works as associated professor at the Inorganic and Organic Chemistry Department.

Objective of the collaboration

The represented institution is looking for a collaboration that leads to a commercial exploitation of the presented invention. The form, terms, and conditions of the collaboration can be openly discussed if the presented technology is of interest. The main goal is to bring this technology to the market, therefore, all support and guidance that help developing the technology in a pathway towards clinical application is welcome.

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