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The Combination of Laser Therapy and Metal Nanoparticles in Cancer Treatment Originated From Epithelial Tissues: A Literature Review

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Abstract

Several methods have been employed for cancer treatment including surgery, chemotherapy and radiation therapy. Today, recent advances in medical science and development of new technologies, have led to the introduction of new methods such as hormone therapy, Photodynamic therapy (PDT), treatments using nanoparticles and eventually combinations of lasers and nanoparticles. The unique features of LASERs such as photo-thermal properties and the particular characteristics of nanoparticles, given their extremely small size, may provide an interesting combined therapeutic effect. The purpose of this study was to review the simultaneous application of lasers and metal nanoparticles for the treatment of cancers with epithelial origin. A comprehensive search in electronic sources including PubMed, Google Scholar and Science Direct was carried out between 2000 and 2013. Among the initial 400 articles, 250 articles applied nanoparticles and lasers in combination, in which more than 50 articles covered the treatment of cancer with epithelial origin. In the future, the combination of laser and nanoparticles may be used as a new or an alternative method for cancer therapy or diagnosis. Obviously, to exclude the effect of laser's wavelength and nanoparticle's properties more animal studies and clinical trials are required as a lack of perfect studies.

Keywords: Nanoparticles; Cancer, Therapy-related; Laser.

Introduction

LASER, despite its history, is recognized as a new technology worldwide. Also, nanotechnology is one of the most recent fields of science. These two technologies, with their specific characteristics, have played a major role in medicine and dentistry. Simultaneous use of these two technologies has created a new approach to modern medicine and dentistry, like diagnosis and treatment of cancer, drug releasing systems, rapid medical testing, tooth sensitivity treatment and improving the adhesion to tooth structure in dentistry.

Recent investigations showed that there has been an increase in the prevalence of cancers. According to GLOBACON (related to World Health Organization) there were about 12.7 million patients suffering from cancer worldwide in 2008 (excluding non-melanoma skin cancer) which is expected to reach 21 million by 2030. This increase requires new treatment methods to be developed.

Cancers are classified based on different aspects such as classification according to the cell origin. Carcinoma includes cancers originating from epithelial cells (e.g., epithelial squamous cell cancer), or the cells that cover the internal organs (such as lung cancer) or glands (e.g. breast cancer). Sarcoma refers to cancer originating from mesenchymal tissues such as bone and muscle. Leukemia and lymphoma include cancers originating respectively from blood-forming and immune cells.[1]

Several methods have been used to treat cancers, including surgery, chemotherapy, radiation therapy, etc. Nowadays, with the recent advances in medical science and new technologies, novel methods have been introduced such as hormone therapy, photodynamic therapy (PDT), treatments using nanoparticles and eventually combinations of lasers and nanoparticles. PDT depends on the availability of oxygen in tumours, but in methods using lasers and nanoparticles, there is no such limitation and they can be used as alternative methods.

Nano technology refers to work at the atomic, molecular and supra-molecular levels (scale of 1-100 nm) in order to

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understand, create and make use of materials, structures, devices and systems with fundamentally new properties and functions due to their small structure.[2]

Nanomaterials are classified based on various parameters including material, size (dimension), shape, etc. with each of them have different applications. Today, nanoparticles (which are the nanomaterial with 3 dimensions) with unique characteristics and tunable optical properties provide valuable cell therapy methods. Great progress has been made in the use of metal nanoparticles for biomedical applications due to their unique size and shape properties.[3-6] Among metallic nanoparticles, gold and silver nanoparticles are highly regarded with increased use in biomedical field.[3,7,8]

Nanoparticles are most widely used in the biomedical fields for diagnosis and treatment of cancer. Treatment of tumours surrounded by vital tissues is problematic and there is a probability that tumour margins remain unclear. On the other hand, cutting healthy tissues may lead to unacceptable beauty and medical results. Application of nanoparticles provides a high degree of accuracy. On the other side near infrared (NIR) radiation is an interesting energy source as human blood and body tissues have the minimum absorption in this wavelength, thus deeper tissues can be reached.[9]

The unique features of lasers such as photo-thermal properties and the extremely small size of nanoparticles (which creates new physical effects that are mainly a result of domination of the quantum properties in contrast to classical properties), provide an interesting combined therapeutic effect. Thermal therapy procures a fast recovery, shorter hospital stay, less complications and is easy to perform.[10]

There are a variety of nanoparticles, and each has its own unique properties and applications such as nanorings, nanoshells, nanorods, nanopores and nanowires, etc. Depending on the peak absorption of nanoparticles, different lasers are used. For example researchers have investigated NIR-tunable nanostructures (nanoshells,[11-13] nanorods,[14] and nanoclusters,[13,15] etc) for photo-thermal functionality.[16]

In fact nanoparticles that have been synthesized to date, have the most absorption in the wavelength range of 600-1200 nm (laser diode). In the future, nanoparticles with maximum absorption in other wavelengths may be synthesized.

Liver, spleen and kidneys are sites that are most effected by nanoparticles.[17] Morbidity and renal complication are the cause of use of gold nanoparticles modified with certain thiol monolayers such as tiopronin.[18] Variable toxicity of nanoparticles is achieved through different size and the material which coats them. For example glutathione-coated gold nanoparticles have 100% survival rate even at concentrations up to and including 60 μM.[18] Investigations show that nanoclusters with smaller size can effectively reduce their toxicity.[17,19] The excretion of nanoparticle is through renal clearance.[17]

The aim of this study was the review of the literature in which lasers and nanoparticles were used simultaneously to treat cancers with epithelial origin.

Results

A thorough search in electronic sources Science Direct, PubMed, Google Scholar was performed for clinical articles between 2000 and 2013 with the following keywords "Au nanoparticle," "Ag nanoparticle," "Cancer therapy," "Laser," and "Combination of Au/Ag in cancer therapy." Overall, 400 articles were found in relation to nanoparticles and lasers topics, among which 250 articles used nanoparticles and lasers in combination while in more than 50 articles nanoparticles and laser were used together in the treatment of cancer with epithelial origin. Most of these studies addressed breast cancer but could be extended to oral tumours.

After assessment of the articles, they have been categorized into different groups based on the type of nanoparticles used in combination with lasers.

Studies on Gold Nanoparticles (Au) Use in Combination With Laser

As mentioned above great progresses have been made in the use of metal nanoparticles especially gold. Because of their unique properties which depend on their size and shape, nanoparticles are used for medical purposes. Among different nanostructures gold nanoparticles are the most appropriate candidate in photothermal sensitizing for the following reasons: they powerfully absorb laser light, are nontoxic, easily conjugates with proteins and antibodies and have tunable optical properties.[3]

Different types of nanoparticles were used in various experiments which consisted of silica gold nanoshells, gold nanorods, gold nanocages, gold-gold sulfide nanoparticles and hollow gold nanoshells. These nanoparticles have good absorption in NIR spectra which provides the most transformation and the least reflection of light in vital tissues. Transformation of nanoparticles can be done in a systemic way (through intravenous injection).[9,10] Many studies have been done in this field.

In Vitro Studies

In 2012, Kuo et al evaluated dual-modality photodynamic therapy (PDT) and photothermal therapy (PTT) by gold nanomaterials conjugated with indocyanine green. Human lung carcinoma malignant cell line (A549) conjugated with Ab_{EGFR}-Au NP of different sizes were irradiated by 808-nm CW diode laser ([22.5 W/cm^2], [20 W/cm^2]) femtosecond and Ti:sapphire femtosecond laser (700 nm) at 2 mW for 10 minutes integration. PTT and PDT killed cancer cells in an efficient manner.[20]

Kessentini and Barchiesi compared quantitatively optimized nanorods, nanoshells and hollow nanospheres for PTT. Several study groups consisting of shallow cancer (e.g. skin cancer) and deep cancer conjugated with different types of nanoparticles: (1) nanorods: (*a*) spheroid (*b*) cylinder (*c*) capped cylinder, (2) nanoshells, and (3) hollow nanospheres (different sizes). The samples were

exposed to pulsed laser (633 nm laser [shallow cancer] and 800 nm [deep cancer]). They found that the hollow nanospheres are more efficient for shallow cancer therapy; whereas hollow nanospheres and nanorods, present similar absorption efficiencies for deep cancer therapy.[21]

In 2011, Fekrazad et al investigated the use of anti-HER2 immuno-nanoshells in treatment of oral squamous cell carcinoma. HER2-positive KB cells and HER2-negative HeLaS3 were bound with gold-silica nanoshell conjugated with anti-her2 (100 nm) and then exposed to laser irradiation at 810 nm and 4 W/cm^2 for 2 minutes. Significant cell death in the KB tumour cell cultures was reported, while there was no evidence of cellular damage or death in the HeLaS3.[22]

Day et al[23] investigated the diagnosis and treatment of cancer by antibody-conjugated gold-gold sulfide nanoparticles. SK-BR-3 breast carcinoma conjugated with ant ti-HER2 antibodies conjugated GGS-NPs was exposed to an 800 nm pulsed laser, consisting of low laser powers (1 mW) for making image and high laser powers (50 mW) for inducing cancerous cells to death. Regarding this study, imaging and therapeutic capability of nanoparticles depended on the amount of laser power.[23] Other studies in this area have been summarized in Table 1.

Animal Studies

Considering the positive results of several in vitro studies, researchers have continued their work on animal models. In 2012, Ma et al showed that Au capped magnetic core/mesoporous silica shell nanoparticles have a synergistic influence of mixed chemo- and photo-thermo therapy. Human breast cancer MCF-7 cells which were seeded in 96-well plate were exposed to 808 nm high power multimode pump laser at a power density of 2.0 W/cm^2 with a beam diameter of 5 mm for 5 minutes. A synergistic effect in loosing viability of cancer cells was reported. They also evaluated this effect in an in vivo study. Walker 256 cells were implanted into SD mice and Au NRs were injected into the tumours under anaesthesia. Then the mice were irradiated by 808 nm high power multimode pump laser (beam diameter of 5 mm and power density of 2.0 W cm^{-2}) for 5 minutes. They could lower the dosage of anti-cancer drug through the synergistic effect, so the toxicity of the drug was limited.[25]

In 2011, Xie et al showed that Integrin αvβ3-targeted gold nanoshells increase tumour vasculature-specific imaging and therapy. HNSCC cell line SCC-4 were inoculated subcutaneously in nude rats for PET imaging for setting up an HNSCC xeno graft model. Then 64Cu-NS–RGDfK was injected into the rats' tail veins and PET imaging was done. For thermoablation analysis the subcutaneous colorectal cancer xeno graft was performed in nude mice, using HCT116 human tumour cells. Then, NS–PEG5K and NS–RGDfK solutions were injected via the tail vein (in each group 2 mice) and mice were exposed to 808 nm NIR laser light with a spot size of 1 cm and 1.2 W 75% duty cycle. Improvement of tumour targeting by conjugation of NSs to cyclo (RGDfK) was seen in all test groups. However, more tumour necrosis was observed in subablative group.[49] Similar studies are summarized in Table 2. Accordingly, it can be concluded that gold nanoparticles and lasers can be used in the treatment of cancer.

Studies Using Silver Nanoparticles (Ag) in Combination With Laser

Prominent for their antibacterial and wound healing behaviour, silver nanoparticles have lately made their way into cancer therapies.[65] When tested on living cells, they were captivatingly shown to have dual activity, inhibiting the growth and the division of tumour cells and their nuclei, while being biocompatible for the healthy ones.[66,67] Further recent results exemplify that silver nanoparticles with different sizes could enhance magnetic induced thermo-sensitivity of glioma cells depending on their size.[68]

In Vitro Studies

In 2011, Boca et al investigated chitosan-coated triangular silver nanoparticles as a novel set of biocompatible and very effective photo-thermal transducers for in vitro cancer cell treatment. In this study they reported the performance of newly synthesized chitosan-coated silver nano-triangles (Chit-AgNTs) with strong resonances in NIR to operate as photo-thermal agent against a line of human non-small lung cancer cells (NCI-H460). The results revealed a novel class of biocompatible plasmonic nanoparticles with high potential to be implemented as effective phototherapeutic agent in the battle against cancer.[65] As these studies (Table 3) show, silver nanoparticles are effective in cancer therapy.

Combination of Au/Ag

Only two papers have discussed the application of laser with a combination of silver and gold nanoparticles, probably because of the similar advantages of both elements.

In 2008, Huang et al investigated the effect of selective PTT on mixed cancer cells, using aptamer-conjugated nanorods. To reach this aim they designed an aptamer-based nanoparticle, which could treat targeted cancer cell selectively and efficiently. They also showed that in contrast with other nanomaterials such as gold nanorods or nanoshells which need high power of laser irradiation, this combination of Au-Ag nanorods requires less laser irradiation to induce cell death in cancerous tissues.[71]

In 2008, Hu et al investigated core-free nano structured Au_xAg_{1-x} dendrites as a new therapeutic agent in treatment of cancer. Two types of $Au_{0.3}Ag_{0.7}$ and $Au_{0.06}Ag_{0.94}$ capped with anti-EGFR antibodies were used in this study. They both showed good biocompatibility. After irradiating maє lignant lung cancer cells A549 with NIR laser (800 nm), cell viability reduced dramatically in cultures treated by anti-EGFR conjugated with $Au_{0.3}Ag_{0.7}$ dendrites, while the laser power was in the range of 10–15 W cm^{-2}.[72] Other similar studies have been summarized in Table 4.

Discussion

The combination of nanoparticles and laser therapy elim-

Table 1. Au Nanoparticles (In Vitro Studies)

Author/Year	Target Cells	Laser Characteristics	Nanoparticle Characteristics	Results	
Botella et al (2012)[24]	42-MG-BA human glioma cells	femtosecond pulse laser irradiation of 790 nm	Plasmonic gold nanoclusters 15 nm diameter gold colloids protected with a thin silica layer	Cell death induced by thermal mechanism and mechanical disruption of the membrane cell; The incorporation of 20(S)-camptothecin within the pores of the external shell, provoked significant cell death increase.	+
You et al (2012)[8]	1. Human MDA-MB-231 breast cancer; 2. A2780 ovarian cancer cells	NIR light	DOX@PEG-HAuNS ratio of 1:3:1 (NP3)	In vitro, NP3 mediated PTA of both cancer cells and DOX release upon NIR laser treatment. In vivo, NP3 showed slower clearance in blood and greater accumulation in tumours than free DOX; Greater antitumour activity; Significantly decreased systemic toxicity; Enhanced antitumour effect	+
Ma et al (2012)[25]	Human breast cancer MCF-7 cells	808 nm high power multimode pump laser; Beam diameter = 5 mm; Power density of laser = 2.0 W/cm^2; 5 min	Au NRs-MMSNEs 200 nm 300 nm	Synergistic effect between the chemotherapy and thermotherapy; We could lower the dosage of DOX by heating the tumour up to a moderate temperature, in this way both the dosage-limiting toxicity of the drug and tissue damage by superheating can be effectively prevented.	+
Sun et al (2012)[4]	1. SK-BR-3 2. Control HTB-22 carcinoma cells	Low laser power of 540 J (3 W/cm^2 for 3 min) 817 nm laser (Coherent, Santa Clara, CA)	GGS-NP-PEG ProG-anti HER-2 IgG 87.8 ± 7.3 nm	Serious death of SK-BR-3 cells	+
Kessentini and Barchiesi (2012)[21]	Shallow cancer (e.g. skin cancer) - Deep cancer	Pulsed laser -633 nm laser (shallow cancer) -800 nm (deep cancer)	1. Nanorod: (*a*) Spheroid (*b*) Cylinder (*c*) Capped cylinder; 2. Nanoshells; 3. Hollow nanospheres (different sizes)	For the shallow cancer therapy, the hollow nanosphere seems to be more efficient; Hollow nanosphere and nanorod, offer comparable absorption efficiencies, for deep cancer therapy.	+
Kuo et al (2012)[20]	Human lung carcinoma malignant cell line (A549)	808-nm CW diode laser (22.5 W/cm^2) (20 W/cm^2) Femtosecond - Ti:sapphire femtosecond laser (700 nm) at 2 mW for 10 min integration	Au-PEI-ICG NPs- Ab_{EGFR}-Au NP: 50 ± 2.31 nm; 100 ± 2.87 nm; 13 nm; Au NR: aspect ratio of 3.8 (length: 35 nm, width: 9.3 nm)	Photochemical destruction ability have increased depending on sizes of Au NPs; Higher temperatures; PTT and PDT efficiently killed cancer cells; Enhanced photo destruction photo stability.	+
Fekrazad et al (2011)[22]	1. HER2-positive KB cells 2. HER2-negative HeLaS3	laser light (Med Art, Hvidovre, Denmark) at 820 nm and 4 W/cm^2 - 2 minutes	Gold-silica nanoshell conjugated with anti-her2 nanobody 100 nm	1. Significant cell death occurred in the KB tumour cell cultures 2. No evidence of cellular damage or death in the HeLaS3 cell cultures	+
Qin et al (2011)[26]	Breast cancer cell line MDAMB-231	(λ0 = 532 nm) of aNd: YAG laser (Brilliant B, Quantel, Inc.); 10 × 6-ns pulses of the laser (10 Hz frequency, intensity up to 400 mJ/pulse; Mean power density of 3.3 W/cm^2)	Dox-PPL/GNPs 50 nm	Significant viability decrease	+
Baeket al (2011)[27]	1. Human grade IV glioma cell line (ACBT); 2. Murine Ma P388-D1 (ATCC, CCL-46)	810 nm laser light (Coherent Inc., Santa Clara, CA) Irradiances=2 to 28 W/cm^2 Spot size= 3 or 5 mm diameter - 1, 5 or 10 min.	Gold nanoshells consisted of a 120 nm silica core with a 12–15 nm gold shell (Nanospectra Biosciences, Inc., Houston, Texas). - PEGylated	Laser treatment not only caused the destruction of the loaded Ma but also was toxic to the surrounding tumour cells; Macrophages readily traverse the patent BBB	+
Beqa et al (2011)[28]	1. Human breast cancer SK-BR-3 cell line; 2. MDA-MB breast cancer cell line; 3. HaCaT normal skin cell line	1.5 W/cm (2) power, 785 nm laser	Gold nano-popcorn attached SWCNT hybrid nanomaterial	Killing of cancer cells very effectively	+
Melancon et al (2011)[29]	Overexpress EGFR: 1. A431 cells and oral cancer cells, FaDu, OSC19; 2. HN5	Continuous-wave GCSLXe05-1600m-1 fiber-coupled diode laser (DHC; China Daheng Group, Beijing, China) with a center wavelength of 808 ± 10 nm. Laser power of 36 W/cm^2 for 3 min	C225-SPIO@Au NS have an average a diameter of 82 4.4 nm, contain 142 15 antibodies per nanoshell	Only the targeting agent, C225-SPIO@Au NS ,caused cell death lyses; Selective targeting with thermal ablation of OSCC	+

Table 1. Continued

Van de Broek et al (2011)[30]	HER2 positive SKOV3 cells: 1. breast cancer cells 2. ovarian cancer cells	38 W/cm(2) using a 690 nm continuous wave laser 5 min	Anti-HER2 targeted branched gold nanoparticles =nanobody conjugated branched gold nanoparticles	Cell death is observed	+
Luo et al (2011)[31]	CCRF-CEM (T-cell acute lymphoblastic leukemia) cells	Plasmon-resonant light (532 nm)	Aptamer/hairpin DNA-gold nanoparticle (apt/hp-Au NP) Dox loaded onto the AuNP	Aptamer-functionalized hp-Au NPs can be used as carriers for targeted delivery of drugs with remote control capability by laser irradiation with high spatial/temporal resolution.	+
Choi et al (2011)[32]	Cancer cells	NIR light	1.nanoshells; 2.nanorods; 3.nanocages	Enhanced accumulation of gold nanostructures to the target cancer as well as for an effective cancer cell ablation.	+
Melancon et al (2011)[43]	Solid tumours	NIR	1.Hollow gold nanospheres, 2.magnetic core-shell gold nanoshells, 3.semiconductor copper monosulfide NPs	Hollow gold nanospheres are used to mediate controlled drug release.	+
Lukianova-Hleb et al (2011)[33]	1. (EGFR)-positive lung carcinoma cells (A549); 2. EGFR-negative normal cells, fibroblasts	Laser pulses (532 nm, duration 0.5 and 10 ns) (STA-01 SH; Standa Ltd., Vilnius and LS-2132, Lotis TII, Minsk, Belarus) with the beam diameter 20 mm (0.5 ns, 116 mJ/cm^2), (0.5 ns, 220 mJ/cm^2), (1.5, 3, and 5 J/cm^2)	PNB generation threshold is determined by the aggregation (clustering) of gold NPs - Different size to 250 nm	Plasmonic nanobubbles were shown to provide precise, tunable, selective, and guided ablation of tissue at a microscopic level	+
Raji et al (2011)[3]	Human epithelial cancer cell line A431	10 mW (diode laser 540 nm)	1. Citrate capped AuNPs; 2.anti-EGFR conjugated AuNPs - Average size 15 nm	Immuno-targeted nanoparticles could selectively induce cell death via ROS mediated apoptosis when cells were exposed to a low power laser light.	+
Carpin et al (2011)[34]	Three HER2-overexpressing breast cancer cell lines: 1. SK-BR-3 2. JIMT-1 3. BT474 AZLR	Femtosecond mode locked Ti:sapphire laser (Coherent, Santa Clara, CA, USA) 808-nm NIR diode laser at 80 W/cm^2 with a 1.5-mm spot size for 5 min.	Silica–gold nanoshells conjugated with anti-HER2 The average nanoshell diameter was 150 ± 10 nm	Successful targeting and ablation of trastuzumab-resistant cells	+
Lukianova-Hleb et al (2010)[35]	EGFR-positive lung carcinoma cells (A549)	1. single pulses (532 nm, 0.5 ns); 2. pulsed probe laser (690 nm, 0.5 ns); 3. continuous probe laser (633 nm, 1mW); 4. pulsed laser (532 nm, 10 ns,1 mJ cm^{-2})	gold spheres of 50 nm and their conjugates with (EGFR) plasmonic nanobubbles (PNB)	The PNBs acted as tunable theranostic agents at the cellular level and in one process that have supported diagnosis, therapy and guidance of the therapy.	+
You et al (2010)[36]	MDA-MB-231 cells	NIR laser centered at 808 nm at an output power of 2.0 W/cm2 for 3 min (Diomed 15 plus, Cambridge, UK)	DOX-loaded HAuNS (DOX@HAuNS)= inorganic nanoparticles ~40-nm diameter	Significantly greater cell killing was observed when MDAMB- 231 cells incubated with DOX-loaded HAuNS were irradiated with NIR light, attributable to both HAuNS-mediated photothermal ablation and cytotoxicity of released free DOX.	+
Huang et al (2010)[37]	PC3-PSMA	CW sapphire (Ti:S) laser 800 nm 20 W/cm^2 15 min (2 mm diameter)	(CTAB) gold nanorods mPEG-GNR	Varying therapeutic efficacies cell injury/death	+
Wang et al (2010)[38]	avb3-positive/negative cells	532 nm green pulsed Laser 6 ns pulse 120 mJcm^2	RGD-Au-SNPs 118 nm	Au-SNPs exhibited significantly enhanced photothermal effects and were used to demonstrate the targeted photothermal treatment of a subpopulation of cancer cells.	+
Kirui et al (2010)[75]	1. A33-expressing cells 2. A33-nonexpressing cells	1.5.1 W cm(-2) using a 808 nm continuous wave laser diode 2.31.5 W cm(-2)	Gold and iron oxide hybrid nanoparticles (HNP-scFv conjugates)	Flow cytometric analyses of the laser-irradiated A33 antigen-expressing cells show apoptosis-related cell death to be the primary mode of cell death at 5.1 W cm (-2), with increasing necrosis-related cell death at higher laser power.	+

Table 1. Continued

Huang et al (2010)[52]	Cancer cells	1. Continuous wave (CW) 2. Nanosecond pulsed laser	Nanospheres	Cell death can be induced with a single pulse of a nanosecond laser more efficiently than with a CW laser. While the CW laser induces cell death via apoptosis, the nanosecond pulsed laser leads to cell necrosis	+
Au et al (2010)[39]	SK-BR-3 human breast cancer cells	-NIR laser with a spot size of 2 mm; femtosecond-pulsed laser (home-built Kerr; lens mode-locked Ti:sapphire laser); bandwidth of 54 nm, a pulsed repetition rate at 82 MHz; - power density = 4.7 W/cm	Gold nanocages PEGylated with OPSS-PEG-SC in an anti-HER2 solution	Better detection of blood vessels and sentinel lymph nodes	+
Day et al (2010)[23]	SK-BR-3 breast carcinoma	800 nm pulsed laser 1 mW and 10 mW; pulsed 810 nm Ti:sapphire laser; 543 nm laser	Anti-HER2 antibodies conjugated GGS-NPs 63.4 nm	Extensive membrane blebbing leading to cell death.	+
Wang et al (2009)[40]	Human breast cancer cells (SK-BR-3 cells)	Laser irradiation (4.53 W/cm^2) 785 nm NIR laser	Aurod–Fe3O4 nano-pearl-necklaces (abbreviated as Aurod–(Fe3O4)n, where n>5) were further stabilized with thiol-modified poly(ethylene glycol) capped with COOH groups hydrodynamic size was approximately 87 nm	Herceptin-conjugated Aurod–(Fe3O4) nanoprobes were used to target SK-BR-3 cells. The tumour targeting probes was successfully demonstrated by dual-mode imaging, single-nanoparticle intracellular dynamics monitoring, and photothermal ablation studies. Then an oprobes were shown to be magnetically and optically active and are therefore useful for simultaneous magnetic and optical detection.	+
Melancon et al (2009)[41]	Human squamous carcinoma A431 cells over expressing EGFR	NIR laser light (808 nm) (~8 W/cm^2) 15 min 40 W/cm^2 for 5 min	anti-EGFR-HAuNS ~30 nm	Anti-EGFR-HAuNS could be delivered to EGFR-positive tumours at (per vascular area of the tumour) 6.8% of injected dose per gram of tissue.	+
Liu et al (2008)[42]	A549 human lung cancer cells	633-nm laser at different power levels 3.75 mW	(lg) G-conjugated gold nanospheres (40 nm)	The death rates after gold nanoparticle exposure increased significantly under laser irradiation	+
Bernardi et al (2008)[43]	1. Medulloblastoma and Daoy.2, a clonal derivative of Daoy that overexpressesHER2 2. high-grade glioma U373 (ATCC) and U87 (ATCC)	800 nm and 80 W/cm^2 for 2 min	Nanoshells ~100 nm conjugated with (PEG) and antibodies: 1. HER2 (Ab-4, clone N12) 2. IL13Ra2 (clone B-D13)	1. Bare nanoshells induced cell death in the area treated with the laser in both the medulloblastoma cell line Daoy, and in the HDF control cells.; 2. Bare nanoshells induced cell death in the area treated with the laser in both the IL-13Ra2 expressing glioma cell line, U373, and in A431 cells, which do not express detectable IL-13Ra2.	+
Huang et al (2007)[44]	HSC oral cancer cells cultured on 18 mm glass coverslips in a 12-well tissue culture plate	Ti:sapphire laser 800 nm pulse duration of 100 femtoseconds repetition rate of 1 kHz	Spherical gold nanoparticles conjugated to anti-EGFR antibodies 30 nm gold nanospheres (λmax=525) are	The laser power threshold for the photothermal destruction of cells after the nanoparticle treatment is found to be 20 times lower than that required to destroy the cells without nanoparticles. The number of dead cells shows a nonlinear dependence on the concentration of gold nanoparticles.	+
Stern et al (2007)[45]	Two human prostate cancer (PCa) cell lines: 1. PC-3; 2. C4-2	NIR light (810 nm, 88 W/cm^2) 5 minutes	Nanoshells	Cells treated with GNS + NIR demonstrated a laser-specific zone of cell death.	+
El-Sayed et al (2006)[46]	Two oral squamous carcinoma cell lines: 1.HSC 313; 2.HOC 3 Clone 8; 3.one benign epithelial cell line (HaCaT)	CW visible argon ion laser at 514 nm - 76, 64, 50, 38, 25 and 19 W/cm^2 - 64, 57, 51, 45, 38, 32, 25, 19 and 13 W/cm^2 at different regions for 4 min	Anti-EGFR antibody conjugated gold nanoparticles 40 nm	No photothermal destruction is observed for all types of cells in the absence of nanoparticles at four times energy required to kill the malignant cells with anti-EGFR/Au conjugates bonded.	+
Huang et al (2006)[14]	1. A nonmalignant epithelial cell line (HaCat) -two malignant oral epithelial cell lines: 1.HOC 313 clone8; 2.HSC 3	Continuous red laser at 800 nm	Anti-EGFR antibody-conjugated nanorods	After exposure to continuous red laser at 800 nm, malignant cells require about half the laser energy to be photothermally destroyed than the nonmalignant cells.	+

Table 1. Continued

Lowery et al (2006)[47]	SK-BR-3 breast carcinoma cells	NIR laser irradiation (Coherent, 820 nm, 0.8 W/m2 for 7 min)	Nanoshells had a 110 nm core diameter with an 11 nm thick gold shell PEG-conjugated anti-HER2/neu was added	Anti-HER2 immuno-nanoshells bound to HER2-expressing cells resulted in the death of SK-BR-3 cells after NIR exposure only within the irradiated area.	+
Zharov et al (2005)[15]	MDA-MB-231 breast cancer cells	Laser pulse (420–570 nm and 1064 nm; 8–12 nanosecond; 0.1–10 J/cm^2) Nd:YAG laser 1064 nm and 532 nm,a 12-nanosecond pulse width - two CW lasers (Pt&Ar): (1) a "Novus 2000" (Coherent, Palo Alto, CA), with a 514-nm wavelength, at 1 W, and a 2-minute exposure; and (2) a "Diomed25" (Diomed, Andover, MD), with an 805-nm Wavelength, at 3 W, for 2 min. CWAr laser at 514 nm, and an IR diode laser at 805 nm.	40 nm gold nanoparticles nanoparticle sizes (20, 40, 60, 100 nm and 130-nm nanoshells)	A significant increase in laser-induced bubble formation and cancer cell killing was observed.	+
Loo et al (2004)[48]	SKBr3 breast cancer cells	Laser emitting light at 820 nm at a power density of ~35 W/cm^2 for 7 minutes	Nanoshells : 1. 120 nm silica core radius with a 35 nm thick gold shell; 2. 100 nm core radius and 20 nm thick shell.	The potential of nanoshells in cancer imaging and therapy.	+
Hirsch et al (2003)[11]	Human breast carcinoma cells =SK-BR-3 cells (ATCC)	NIR light (820 nm, 35 W/cm^2)	Nanoshells 55-nm core radius and a 10-nm-thick shell	Circular regions of cell death are seen in fluorescence microscopy images.	+
Cheng FY (2009)[76]	1-A549 lung cancer cells 2- HeLa cervix cancer cells 3- TCC bladder cancer cells	CW NIR laser 808 nm laser	1-silica@Au nanoshells 2-hollow Au/Ag nanospheres 3-Au nanorods	The photothermal efficiency rankings are silica@Au nanoshells> hollow Au/Ag nanospheres> Au nanorods. Additionally, we found that HeLa cells seem to present better heat tolerance than the other two cancer cell lines.	+
Abdulla-Al-Mamun M (2009)[77]	HeLa cell	Continuous visible light at 400-600 nm with UV- and heat-cutoff filters	Gold colloidal nanoparticles were prepared by the liquid laser ablation of a gold metal plate in water and also by the citrate reduction of HAuCl(4).4H2O	The distinct cell-killing effect was observed	+

Table 2. Au Nanoparticles. In Vivo Studies (Animal Studies)

Author/ Year	Target Cells	Laser Characteristics	Nanoparticle Characteristics	Results	
Ma et al (2012)[25]	Walker 256 cells (5×10^6 cell/site) were implanted subcutaneously into SD mice.	-808 nm high power multimode pump laser -beam diameter = 5 mm and the; Power density of laser; source was fixed at 2.0 W cm^{-2}; 5 min	Au NRs-MMSNEs 200 nm 300 nm	From the synergistic effect between the chemotherapy and thermotherapy of the drug-loaded Au NRs-MMSNEs-DOX-NIR, we could lower the dosage of DOX by simply heating the tumour up to a moderate temperature, in this way both the dosage-limiting toxicity of the drug and tissue damage by superheating can be effectively prevented.	+
Kennedy et al (2011)[9]	Mouse	NIR	Gold colloidal nanospheres (40-45 nm)	The use of T cell chaperones for AuNP delivery could enhance the efficacy of nanoparticle-based therapies and imaging applications by increasing AuNP tumour accumulation.	+
Bardhan et al (2011)[50]	Subcutaneous breast cancer tumours in animal models	1. Near-infrared fluorescence 2. Magnetic resonance imaging (MRI)	Gold nanoshells, spherical nanoparticles with silica cores and gold shells DNA-conjugated nanoshell	Double-stranded DNA nanoshells also provide a way to deliver small molecules into cells	+
Huang et al (2011)[51]	Clinical trial	Laser	1. Gold Nano rod elastin-like polypeptide matrices. The matrices were also loaded with the heat-shock protein (HSP)90 inhibitor 17-(allylamino)-17-demethoxygeldanamycin (17-AAG) 2. without (17-AAG)	The combination of hyperthermic temperatures and the release of 17-AAG from the matrix, both induced by laser irradiation, resulted in significant (>90%) death of cancer cells, while 'single treatments' (i.e., hyperthermia alone and 17-AAG alone) demonstrated minimal loss of cancer cell viability (<10%).	+
Choi et al (2011)[78]	Not mentioned	NIR laser	GNRs were loaded into functional nanocarriers (chitosan-conjugated, pluronic-based nanocarriers)	Complete tumour resorption was achieved without damage to the surrounding tissue.	+
Rylander et al (2011)[52]	-CB17-Prkd c SCID/J mice -PC3	Wavelength of 810 nm, irradiance of 5 W/cm (2), spot size of 5 mm, and heating duration of 3 min	Gold nanoshells (diameter of 55 nm and outer gold shell thickness of 10 nm)	Laser therapy alone caused significant induction of HSP expression; Laser and nanoshells experienced substantial temperatures (73-78°C) which eliminated HSP expression.	+
Stafford et al (2011)[53]	Xenograft model of prostate cancer (PC-3)	High-power diode lasers 808 nm for 180 s at 4 W/cm(2)	AuNS 140-150 nm	A statistically significant ($P<0.001$) increase in maximum temperature in the tumour cortex (mean = 21 ± 7°C) in +AuNS tumours versus control tumours. Converts the tumour vasculature into a potent heating source for nanoparticle mediated ablation at power levels which do not generate significant damage in normal tissue.	+
Melancon et al (2011)[54]	A431 tumour xenograft of mice	One tumour in each mouse was irradiated with laser at 808 nm (4 W/ cm^2 for 3 min)	C225-HAuNS	C225-HAuNS mediate laser-induced thermal effect in tumours; C225-HAuNS injection followed by laser treatment enhances tumour vascular perfusion	+
Melancon et al (2011)[29]	Mice bearing A431 tumours - nude mice (20e25 g; Harlan Sprague Dawley, Indianapolis, IN)	Laser at a power of 36 W/cm^2 for 3 min	C225-SPIO@Au NS have an average a diameter of 82 4.4 nm, contain 142 ± 15 antibodies per nanoshell	Selective targeting with thermal ablation of OSCC	+
Xie et al (2011)[49]	An HNSCC xenograft model in nude rats subcutaneous inoculation of the HNSCC cell line SCC-4; subcutaneous colorectal cancer xenograft model using HCT116 human tumour cells in nude mice,	1.2 W 75% duty cycle, 808 nm NIR laser and a spot size of 1 cm	Silica core (~120 nm in diameter) and a gold shell (8~10 nm) Integrin αvβ3-targeted gold nanoshells	Greater degree of tumour necrosis	+

Table 2. Continued

Melancon et al (2011)[55]	Mice bearing A431 tumours	NIR light centered at an 808 nm	SPIO@AuNS	Significant temperature elevations when intra tumourally injected and irradiated with NIR light (65.70°C ± 0.69°C vs. 44.23°C ± 0.24°C for saline + laser)	+
Elsherbini et al (2011)[56]	Ehrlich carcinoma implanted in female mice	Diode laser 1.CW λ 535 nm (green), power 0.5–1.0 W, laser fluency 200 J/cm^2 , and duration 15–30 min 2. near infrared light (CW, λ 980 nm, power 1 W/cm^2)	Au@Fe3O4 - core shell nanoparticles 54 ± 3 nm - Fe3O4 size 22–55 nm	In mice treated with gold nanospheres, tumours continued to grow but at a slow rate; more than 50% of the tumours treated with gold-coated magnetic nanocomposites completely disappeared.	+
Wagner et al (2010)[57]	Zebrafish C4-2B prostate cancer (PC) cells	Second pulse with a fluence of 175 mJ/cm^2	Conjugates of gold spheres 60 nm with (EGFR) antibody C225	PNBs were generated specifically in NP-containing individual cancer cells. The PNB-treated embryos were observed for up to seven days and all of them survived the PNBs.	+
Au et al (2010)[39]	Rat	NIR laser with a spot size of 2 mm; femtosecond-pulsed laser (home-built Kerr; lens mode-locked Ti:sapphire laser); bandwidth of 54 nm, a pulsed repetition rate at 82 MHz; Power density = 4.7 W/cm	Gold nanocages PEGylated with OPSS-PEG-SC in an anti-HER2 solution		+
Sirotkina et al (2010)[58]	animal	810 nm	gold nanoparticles	Laser hyperthermia induced apoptotic death of tumour cells and inhibited tumour growth by 104% on the 5th day after treatment.	+
Park et al (2010)[59]	Xenografted MDA-MB-435 human melanoma tumour in mice	Diode laser (I¼ 810 nm, 0.75 W/cm^2) 15 min	1.(CTAB)-coated GNRs were coated with a mixed monolayer of (PEG) average width of 13 nm and length of 47 nm 2. SERS-tagged gold nanoparticles	Pair of synthetic nanoparticles can work together to detect a diseased site and more effectively deliver chemotherapeutics to the site than individual nanoparticle treatments.	+
Goodrich et al (2010)[10]	Murine subcutaneous colon cancer model female Balb/c mice, 5 to 6 weeks of age Taconic, Hudson, New York weighing 16 to 20 g	1. A cooled optical diffusing fiber with an isotropic diffusing tip of 1 cm LDF-10, BioTex, Inc., Houston, Texas, 2. 808-nm laser Diomed 15-plus, Diomed, Inc., Cambridge, UK for 180 s at 3.5-W average power	PEGylated Gold Nanorods Average rod size was determined to be 44.7±5.4 nm (CTAB)	Survival of the photothermally treated group was statistically longer than the control groups. 44% tumour free	+
Elbialy et al (2010)[60]	Mice -Ehrlich carcinoma	CW argon ion laser with irradiance 55 mW cm^{-2} for 45 min	GNPs with an average diameter 13 ± 1.2 nm and optical density (ODlambda:518 nm = 3)	Noninvasive technique for PTT of skin or near-surface type tumours that need much less laser energy and lower concentrations of GNPs. Significant suppression in tumour growth throughout 15 days.	+
Park et al (2010)[61]	Mice bearing bilateral tumours (MDA-MB-435 human carcinoma or C8161 human melanoma)	NIR irradiation (810 nm, ~0.75 W/cm^2) from a diode laser	Gold nanorod, magnetic nanoworm, and Doxorubicin Lipo-Somes = (PEG)-coated NR/LyP-1LP~70 nm	Effective in vivo photothermal heating of the tumour is achieved	+

Table 2. Continued

Lu et al (2009)[62]	Murine B16/F10 melanoma cells	NIR, peak 808 nm low dose energy of 30 J/cm^2	NDP-MSH-conjugated PEGylated HAuNS (NDP-MSH-PEG-HAuNS)(outer diameter, 43.5±2.3 nm; shell thickness, 3–4 nm)	Successful selective PTA of B16/F10 melanoma with targeted HAuNS was confirmed by histological and [18F] FDG-PET evaluation at 24 h post NIR laser irradiation.	+
Melancon et al (2009)[41]	A431 tumours were grown subcutaneously in the right thigh of nude mice	NIR laser light (808 nm) (~8 W/cm^2) 15 min 40 W/cm^2 for 5 min	anti-EGFR-HAuNS ~30 nm -DTPA-C225-HAuNS -DTPA-IgG-HAuNS	Anti-EGFR-HAuNS could be delivered to EGFR-positive tumours at (per vascular area of the tumour) 6.8% of injected dose per gram of tissue.	+
Stern et al (2008)[63]	Nude mice	810 nm near infrared laser with a 200 mu laser fiber and an energy setting of 4 W/cm (2) 3 min	110 nm gold nanoshells with a 10 nm gold shell	93% tumour necrosis and regression in the high dose treated group; The ablation zone was sharply limited to the laser spot size	+
Ji et al (2007)[64]		The laser was a continuous wave GCSLX–05-1600m-1 fiber-coupled diode laser (DHC, China Daheng Group, Inc. Beijing, China) with a center wavelength of 808±10 nm.	PEG-coated SPIO-Au nanoshells - 2-100 nm - average diameter of 82.2 ± 9.7 nm, and the gold shell had a thickness of ~8 nm.	The use of SPIO-Au nanoshells should enhance the efficacy of nanoshell-mediated photo-thermal therapy by making it possible to direct more nanoparticles to tumours through the application of external magnetic field and by permitting real-time in vivo MRI imaging of the distribution of the nanoparticles before, during, and after photo-thermal therapy.	+
O'Neal et al (2004)[12]	Mice Murine colon carcinoma cells (CT26.WT).	Diode laser (808 nm, 4 W/cm^2, 3 min).	PEG coated nanoshells (approximately 130 nm diameter)	All such treated tumours abated and treated mice appeared healthy and tumour free >90 days later.	+
Hirsch et al (2003)[11]	Female nonobese diabetic CB17-Prkd c SCIDJ mice solid tumours	NIR light (820 nm, 4 W/cm^2) 6 min	Nanoshells 55-nm core radius and a 10-nm-thick shell	(ΔT 37.4 ± 6.6°C) within 4–6 min; MRTI calculations reveal an area of irreversible thermal damage	+

inates cancer cells via two mechanisms. First, there are a series of specific molecules such as HER2, ERBB1 on the surface of cancer cells. Initially, antibodies against these molecules are designed, and then nanoparticles are bind to these antibodies. These nanoparticles attached to the antibody and then to the cell surface molecules. The tumour area is irradiated with a laser, which has most absorption in nanoparticles. Laser irradiation causes heat in the gold or silver area and the total heat leads to the selective death of cancer cells. Such mechanism, which can target cancer cells selectively, is not seen in other methods such as chemotherapy and surgery. In fact, this is the advantage of such mechanism.[22,37,39,65]

In the second mechanism murine macrophage is used and it is labeled with cell fluorescent dye PKH26GLred. Then gold nanoshells are loaded to the macrophages under 710 to 820 nm light and the tumour/macrophage hybrid is produced by centrifusion. Afterwards, the hybrid is irradiated with 810 nm laser with the power density of 2- 28 W/cm^2. Laser light not only destroys the macrophages but is also toxic to the surrounding cells.[27]

A brief survey shows that no study has been done on humans and most of the studies have been done in vitro and some of them on animals. The reason might be limited volunteer patients, and the fact that this method is a complicated and novel science. Studies also showed that in treatment of cancer cells the most used nanoparticle are gold (Au) and silver (Ag) nanoparticles or to a lesser extent, a combination of gold and silver nanoparticles. Besides, the highest laser wavelength is in the visible and NIR range (400-1200 nm), so the outcome is related to the optical properties of the biological tissues.

In all in vitro and animal studies, the result of combined use of nanoparticle and laser for therapeutic purposes was the death of cancerous cells and enhancement of tumour contrast for imaging intentions.[3,7,25,38,48]

The type of Laser applied in most of the investigations was NIR with wavelength spectra of 785 nm up to 1046 nm,[4,7,10,15,21,39,40,56,59] with 808 nm wavelength used more frequently.[10,20,25,29,34,41,49,62,72] As mentioned earlier, the 808 nm wavelength was the most effective in studies aiming at photothermal destruction of cancer cells. The absorption peak of gold nanoparticles can be modulated by creating different shapes and size.[73,74]

Another investigated wavelength was in the visible light spectra: 420 nm up to 690 nm.[3,15,21,33,35,38,46,56,70] The application of this wavelength was mostly in generating nanobubbles[15,33,35,38,46] and destruction of cancer cells in nanocomposites system.[21,56] Nd:YAG, Diode laser and Ti:sapphire were such systems. Samples were chosen from epithelial carcinomas including: A431,[3,54] lung carcinoma cells (A549),[20,33,35,72] glioblastoma,[7] SK-BR-3[4,34,39,40,48] and other carcinomas occurring in epithelial tissues. Nanoparticles included gold silica nanoshells,[21,22,27,41,43,48,49] gold nanoparticles,[15,20,46] triangular silver nanoparticles, hollow gold nanospheres,[21,44,54,62] silver dendrimer nanocomposites,[70] gold nanorods,[10,20,21] Au_xAg_x,[72] gold nanocages[39] and gold nanocomposites.[25,29,38,40,56]

Table 3. Ag Nanoparticles (In Vitro Studies)

Author/Year	Target Cells	Laser Characteristics	Nanoparticle Characteristics	Results	
Huang et al (2011)[69]	Liver cancer cells	30 min 2 W, 808 nm laser power density of 1.4 W cm^{-2}	Mean diameter of 83 nm silica-coated plasmonic Pd@ Ag core-shell nanoplates Plasmonic Pd@Ag Core-Shell Bimetallic Nanoplates	~ 100% of the liver cancer cells were killed after irradiation for 5 min with an 808 nm laser providing a power density of 1.4 W cm^{-2}	+
Boca et al (2011)[65]	Human non-small lung cancer cells (NCI-H460)	800 nm wavelength Ti:sapphire laser	Chitosan-coated silver nanotriangles (Chit-AgNTs)	Biocompatible plasmonic nanoparticles with high potential to be implemented as effective phototherapeutic agents in the battle against cancer.	+
Tse et al(2011)[70]	KB tumour cells human epidermoid cancer cell line	NIR femtosecond Three different average laser powers: 1.2 mW, 0.6 mW, and 0.12 mW.	Silver-dendrimer composite nanodevices (CNDs) CNDs [(Ag(0))(25)-PAMAM_ E5.(NH(2))(42)(NGly)(74)(NFA) (2.7)] dendrimer-folic acid (FA) conjugates	Significant reduction in breakdown threshold and thus selectively promoting intracellular laser-induced optical breakdown.	+

Table 4. Combination of Ag & Au Nanoparticles (In Vitro Studies)

Author/Year	Target Cells	Laser Characteristics	Nanoparticle Characteristics	Results	
Huang et al (2008)[71]	(NB-4) cells	8.5 x 10 (4) W/m (2) laser exposure	Au-Ag NRs	Au-Ag nanorod combination offers selective and efficient photothermal killing of targeted tumour cells. The tumour tissue will be selectively destroyed at laser energies which will not harm the surrounding normal tissue.	+
Hu et al (2008)[72]	SK-BR-3 (Her2/neu-positive breast cancer cells) and H520 (Her2/neu-negative lung cancer cells) cells	NIR region 800 nm 35 Wcm^2 for 7 min femtosecond pulse laser Ti:sapphire	Anti-EGFR-conjugated Au(x) Ag(1-x) nanostructures with dendrite morphology and a hollow interior dendrites 400 nm	The hollow $Au_{0.3}Ag_{0.7}$ nano structured dendrites show potential in photo thermolysis for killing cancer cells.	+

Antibodies anti-HER2, anti-EGFR were used the most to conjugate with nanoparticles and acts as nanocarriers.[3,34,35,39,40]

Some studies used macrophages as biocarriers of nanoparticles, through phagocytosis.[7,27] The main tasks of macrophages are to overwhelm and digest alien material of the body, so they easily move due to their migration capability and can simply surround cancer tumours. Besides macrophages are exceedingly located inside and around cancer tumours, while some studies show that up to 30% of cancer tumours consist of macrophages.[7,27]

Most studies used gold as the only nanoagents. These nanoparticles powerfully absorb laser light, are nontoxic, easily conjugates with proteins and antibodies, and have tunable optical properties.[3] Two studies focused their investigations only on silver nanoparticles[65,70] that were also effective in cancer therapy, but no study compared gold only and silver only nanoparticles with each other. Two studies investigated the combination of gold and silver as a unit agent,[71,72] which showed better performance than gold alone.

Disadvantages of lasers and nanoparticles combined therapy include high cost and difficulty finding identical particles. Besides, it requires complicated and advanced technology which may not be easily obtained.

Conclusion

It can be concluded that laser and nanoparticles together are a novel class of cancer therapy and diagnosis. More studies should be done to identify the most effective nanoparticles and laser wavelength. Also, more animal studies and clinical trials need to be done as mandated by the lack of valid enough studies in this field.

These methods and mechanisms can be used as a treatment modality to aid cure cancers in future.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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