

## Case Report

# Review of Laser in Nanophotonics – A Literature Study for Cellular Mechanism

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## Keywords

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- Photoablation
- Light Emitting Diode

## Abstract

Laser is a monochromatic, coherent, tunable light source available in different wavelength, mode and power. Laser is used in diagnosis and therapeutics in medicine. Photonano therapy (PNT) is an emerging cancer treatment methodology involves the combination of light photons and nanoparticles. Basic approach of this review is defining features of lasers and their breakthrough potential in design and development of cancer treatment. In this review, types of lasers employed to different nanoparticles such as gold, carbon, silica and iron oxide nanoparticles in PNT were discussed. A nanoparticle hit with laser of different wavelength produces different responses in cells. This review explains the modified nano particle response and cell death mechanism by laser parameters. PNT creates hyperthermia, photo ablation, vaporization, carbonization and apoptosis in cells based on nanoparticles and light source combination. Over these years, cancer-targeting treatment has been greatly improved by new tools and approaches based on nanotechnology. In contrary, 66 articles were studied to understand the role of lasers in cancer therapy. Laser wavelengths ranging from 514 to 980 nm were discussed in this review. Also we discussed the general principle of intracellular mechanisms, size and shape of nanoparticles employed for PNT.

## ABBREVIATIONS

PDT: Photodynamic Therapy; LASER: Light Amplification and Stimulated Emission of Radiation; LED: Light Emitting Diode; PNT: Photo Nano therapy; PTT: Photo Thermal Therapy; GNP: Gold Nanoparticles; UV: Ultra Violet; NIR: Near Infra Red

## INTRODUCTION

Laser can be used as a pointer against a wall, can drill a hole in a hard metal and efficiently be able to cut diamond. The origin of light for therapy in medicine and surgery can be traced from ancient times [1]. Laser, the acronym for light amplification by the stimulated emission of radiation (LASER), is an optical source that emits photons as a coherent and narrow beam of light. In 1917, Einstein predicted that atoms could be stimulated to emit light using Bohr's theory of optical resonators. Around 40 years later, Maiman (1960) construct a device to emit radiation in the visible region of the spectrum. Within a year, visible laser being developed and the first medical application were reported in ophthalmology for treatment of an eye tumor [2]. From there, the application of lasers in medicine has progressed rapidly. Laser is a primary component in various spectroscopes and microscopes. In spectroscopy, laser is used in Raman spectroscopy, optical

coherent tomography (OCT), acoustic spectroscopy, transient absorption spectroscopy, particle size analyzer (PSA), fluorescence life time studies; in microscopy, laser is used in confocal microscopy, laser-scanning microscopy and in fluorescence laser scanning microscopy (FLSM). Laser is a major tool for precise diagnosis and scanning of cells and tissues non-invasively. In cancer therapy, laser based treatment methodology is not universal as in diagnosis and research groups, physicians were applying varying parameters.

Laser has the characteristics of monochromatic, coherence, and collimation [3]. These properties provide a narrow beam of high intensity light, which transmits deep down into the target tissue with minimal power loss and great precision [4]. Laser usage reported for tumor eradication in 1965 followed by wide interest in late 1970s. Laser is available in Ultra violet and Visible (UV-Visible) and Near Infra Red (NIR) wavelength range. Commonly used lasers in medicine are Argon ion laser, Nd: YAG and Carbon dioxide laser [6]. Argon laser sends a very high electric charge through argon gas whereas CO<sub>2</sub> laser known as surgical knife emits 10.6- $\mu$ m wavelengths used in surgery. Nd: YAG laser can penetrate deeply within tissue and emits 1064 nm, 532 nm, 355 nm and 266 nm. Ti: Sapphire is a tunable NIR laser

with wavelength ranging from 650 nm to 1100 nm [7]. Types of laser and their penetration depth in human skin were detailed in figure (1).

### Photo therapy

In cancer therapy, laser is used in phototherapy, low-level laser therapy (LLLT), photodynamic therapy (PDT), photo thermal therapy (PTT) and plasmonic photothermal therapy (PPTT) [8]. Phototherapy began in Ancient Egypt, Greece and India but disappeared for many centuries and was rediscovered at the beginning of the twentieth century [1]. Long ago, it was thought that sunlight was the only aspect in the cure of disorders such as skin cancer and this treatment process is known as phototherapy. As science advanced, it is understood that, there were endogenous substances of the system involved in light therapy, which absorbs light rays leads to the therapeutic responses [9]. Photodynamic therapy (PDT) is a technology that uses a photosensitizer that is activated upon exposure to visible or near infrared (NIR) light, and transfers energy to molecular oxygen, thereby generating reactive oxygen species (e.g., singlet oxygen, free radicals, peroxides), which kills cancer cells [5]. PDT uses photosensitizers in combination with light source to treat premalignant and malignant conditions and conventional photosensitizers have their own side effects. To overcome the disadvantages of photosensitizers, nanoparticles replaces photosensitizers for the last two decades and changes the face of photodynamic therapy. In PDT photosensitizers show both necrosis and apoptotic pathway for cellular destruction through PDT and the balance between these two mechanisms being dependent upon photosensitizers [10]. Whereas in photonanotherapy, range of parameters include light-dose, the concentration of photosensitizer, post-irradiation time, cell type, its genetic and metabolic potential, the nature of the photosensitizer and its sub-cellular localization are need to be explored. This review focuses on significance of laser parameters in photonanotherapy. Invention of laser in 19<sup>th</sup> century paves a new way for the healing power of light.

In photo nano therapy, nanoparticle and laser parameters such as size, shape, laser fluency and mode (continuous wave (CW)/pulsed) determines the cellular mechanism. By binding nanoparticles to targeted cells and by localizing energy deposition into the particles, selective cell damage can be achieved without affecting neighboring cells [11]. Laser and nanoparticles has the potential to offer solutions to the current obstacles in cancer therapy. Nanoparticles were chosen based on size, shape, non-toxicity, binding efficiency, stability, excretion and clearance period from the system. Nanoparticles meets the above criteria, and also have to match laser source, which make the treatment procedure more challenging. For the past two decades, hundreds of nanoparticles with various size and shapes were synthesized however the lasers available only in few wavelengths. In photosensitizer-mediated cancer therapy the laser fluency required for cell lethality (0.5 J/cm<sup>2</sup>) is moderate compared to the fluency used in clinical treatment of pigmented skin lesions (up to 5 J/cm<sup>2</sup>).

In photo thermal therapy nanoparticles such as gold nanoparticles convert optical energy to thermal energy through surface plasmon resonance; Nanoparticles were designed and

synthesized based on laser wavelength; which also restricts the application of nanoparticles. In PNT, mode of cell death varies viz., hyperthermia, apoptosis, micro bubble formation, photo thermal ablation, nano bubble generation, mechanical and acoustic damage to the membranes, membrane blebbing, Deoxy Ribo Nucleic Acid (DNA) damage etc., (Figure 2). The events that take place after the absorption of the laser pulse energy by small particles depend on the size of the absorber and the duration of laser exposure [11]. Laser with long pulses that exceed the thermal relaxation time ( $t_r$ ) of the target molecule i.e nanoparticle, cause heating of both the particle and the surrounding media as heat diffuses across the boundary. If the laser pulse duration is equal to or less than  $t_r$  then the energy can be thermally confined within the target, causing rapid heating of the nanoparticle itself [12].

**Bubble formation and vaporization:** The extreme temperature rise can induce explosive vaporization of a thin layer of fluid in contact with the nanoparticle, creating a vapor bubble that expands rapidly, on the nanosecond timescale as the initial high vapor pressure overcomes the surface tension of the fluid. The lifetime of the bubble is a function of its size at maximal expansion [13].

**What is Nano bubble formation?:** Nano bubbles are generated by laser heated plasmonic nanoparticles. Nano bubble maximal size and lifetime are to a large extent controlled by the ballistic thermal flux, which is present inside the bubble. Laser pulse duration influences, the number of nano bubbles generated and their maximal size [14].

**Hyperthermia:** Small increases in local temperature are known to result in disruption of nuclear and cytoskeletal assemblies and membrane blebbing under hyper thermic conditions. Because of their rapid metabolic rates, tumor cells are regarded as increasingly vulnerable to hyperthermia effects such as disruption of metabolic signaling processes, protein denaturation, and the onset of acidosis or apoptosis caused by the production of heat-shock proteins and other immunostimulants [15].

**Thermal explosion:** There are two main physical mechanism that could lead to explosion of metal nanoparticles particularly GNPs. Thermal explosion mode through electron phonon excitation relaxation and coulomb explosion mode through multiphoton ionization. The mechanical and optical properties of the bubble are determined by its maximal diameter. This in turn depends upon optical energy being absorbed and converted into heat by the plasmonic Nanoparticles [16].

**Cell ablation:** The cell ablation was an immediate mechanical, not thermal phenomenon [17]. Apoptosis is a programmed cell death and necrosis is an accidental cell death mechanism.

Lasers and nanoparticles are more efficient, target specific and harmless to the surrounding healthy cells. The idea of writing this review article came from my research work in cancer treatment using low power laser and gold nanoparticles. In the work, MDCK cells were incubated with gold nanoparticles and irradiated with low power Nd: YLF laser and observed for 72 hours. Initially, laser focus on 1 mm spot size in a 10 mm cell culture well plate and quantified with MTT assay, the results were not accurate.

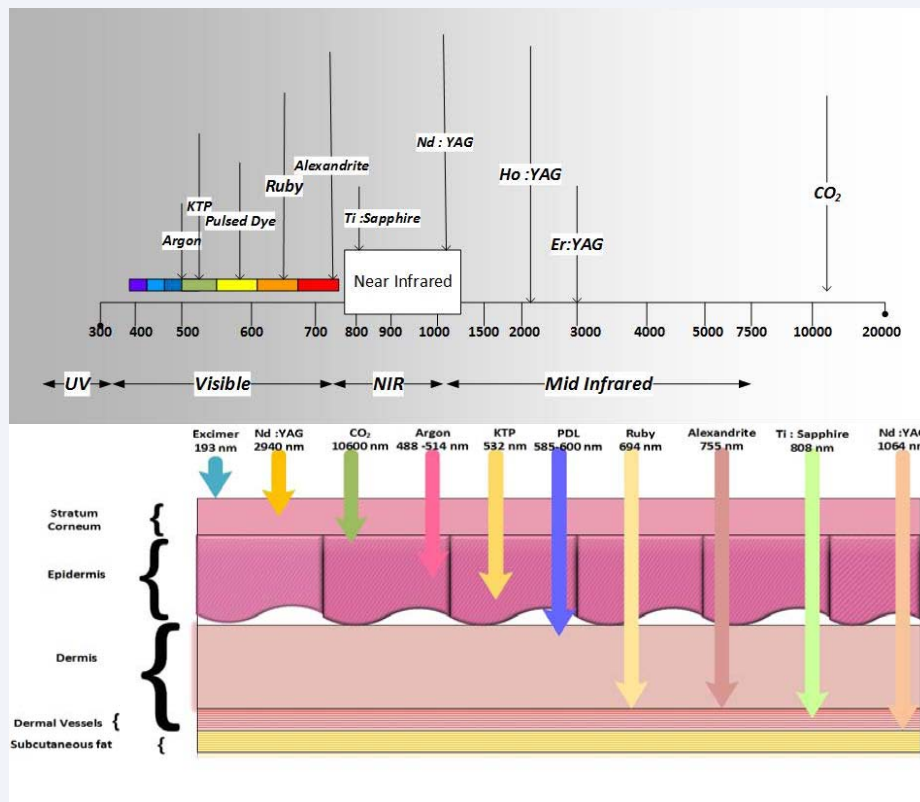


Figure 1 Lasers of UV-Vis -NIR wavelength and CO<sub>2</sub> b. Penetration depth of laser in layers of skin.

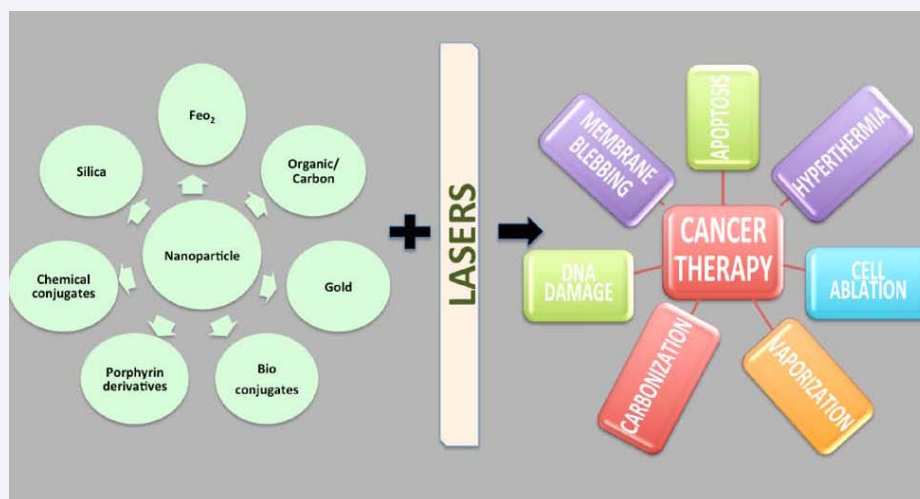


Figure 2 Diagrammatic representation of nanoparticles and cellular mechanism involved in photonanotherapy.

After PPT, MTT assay was performed in adherent cells and the post irradiation changes were observed microscopically. The results show more accumulation of formazan crystals in laser irradiated spot 4 hours after irradiation. Gold nanoparticles and low power laser not induced photo thermal effect in MDCK cells, whereas produce delayed apoptosis instead of thermal effect. While exploring the role of laser parameters, cancer therapy will get advanced well.

## DISCUSSION

Laser parameters and cellular response along with details over the cell lines were listed in table 1. This review covered 66 articles and the significance of laser was discussed. Laser wavelength ranging from 514 nm to 980 nm was also listed in table 1 based on wavelength of irradiation from lower wavelength to higher. Briefly, 500 nm-550 nm laser were used in 7 articles, 640 nm-690 nm in 16, 775 nm-790 nm in 7 groups, 800 nm-820

**Table 1:** Laser and nanoparticles in in vitro cell lines and mechanism of photo nanotherapy.

S. No	Laser Wavelength	Laser mode	Energy	Cell line/ In vivo	Nanoparticles	Size	Nanophotonic effect of laser in cells	Reference
1	514 nm	CW	25 and 19 W/ cm <sup>2</sup> -Malignant/57 W/ cm <sup>2</sup> for benign	Breast cancer cell line (HS578T) / HSC 3 and HOC 313 clone 8 cells/ HaCaT	Anti EGFR Coated gold nanoparticles	40nm	Hyperthermia/Photothermal Therapy	[18]
2	530 nm	ns-pulsed	7 W/cm <sup>2</sup> ,	Ductal carcinoma cells (ATCC: Hs 578T), normal cell line 3T3 Hs578T	Transferrin-conjugated gold nanoparticles	24.7, 44.8 and 50.5 nm 1.3	Thermal energy. The process involves electron-phonon relaxation in the nanoparticles followed by phonon-phonon relaxation, resulting in an increase in the temperature of the cells [26].	[19]
3	532 nm&700-850 nm	CW	200mW	-	Gold nanoparticles	15,30,60,100	Thermal Energy -GNR undergoes melting and shape change when subjected to ultra-short (such as femto-second or nanosecond) laser pulses.	[20]
4	532 nm	CW	0.5, 0.7, and 1.0 W/ cm <sup>2</sup>	CCRF-CEM cells	Dox:hp-Au NP complex hybrid multi- yolk-shell Au-Ag@a-C:H	13 nm	Au NPs absorb laser light, convert it to heat, and then dissipate heat energy to the surroundings, leading to a gradual release of Dox molecules.	[21]
5	532 nm	Pulsed	120 mJ/cm <sup>2</sup>	MCF7,U87	Au-SNP	2 nm	Laser-induced micro bubble-generation	[22]
6	532 nm	-	1.2 J/cm <sup>2</sup>	MDA-MB-231	Mesoporous silica nanoparticles (MSNs) with Pd-porphyrins	100 nm	Cell death mainly caused via necrosis.	[23]
7	632.8 nm/ NIR laser	-	~30 mW/cm <sup>2</sup> for 10 min.	MGC 803 cells stomach cancer	Folic Acid-conjugated Graphene Oxide loaded Ce6 FA-GO-Ce6	<50 nm	The FA-GO-ce6 was endocytosed into cytoplasm and formed endosomes via the folate receptors mediated pathway; (2) When the endosomes were gradually turned into lysosomes, Ce6 was released from FA-GO-Ce6 due to the change of micro-environment in lysosomes (pH 4~5); (3) the released Ce6 got away from the lysosomes into the cytosol. Subsequently, the photodynamic efficacy was achieved upon irradiation of appropriate wavelength and dosage.	[24]
8	CW	637 mW		4T1 murine mammary tumor cell line in BALB/c mice	Multi-dye theranostic silica nanoparticles		Photothermal ablative therapy and tumor necrosis.	[25]
9	647 nm	Dye laser pumped with Ar Ion Laser	3.2 mW/ cm <sup>2</sup>	MDA-MB-435 and 9L cells	Multifunctional Biodegradable Polyacrylamide nanocarriers	44 nm	Multifunctional NPs containing both fluorophores and PS drugs, as well as tumor-targeting moieties, did give bright fluorescence images of specific tumor cells and also generated singlet oxygen, only upon light irradiation, resulting in an irreversible but selective destruction of the cancer cells	[26]

10	Diode laser 660 nm	CW	13 W/ cm <sup>2</sup>	HeLa cells B16 F10 NIH 3T3 cells	Super Gold Nanopar- ticles pH Sensitive	10 nm	Photothermal efficiency with very low fluency	[27]
11	665 nm	Dye pumped Ar Ion Laser	75 mW/ cm <sup>2</sup>	BALB/cAnNCr mice with Co- lon26 c	Photosensitizers Into poly acrylamide nano- particles	29 ±3 nm	Generate singlet oxygen upon light irradiation, which resulted in irreversible de- struction of cells.	[28]
12	665 nm	Dye laser pumped with Ar Ion Laser	3.2 mW/ cm <sup>2</sup> (0.125- 8.0 J)	Colon-26 and RIF-1 cell lines	Organically modified silica (ORMOSIL) na- noparticles	~20 nm	PS generate cytotoxic singlet oxygen molecules upon pho- toirradiation	[29]
13	670 nm	CW	3 W/ cm <sup>2</sup>	Murine renal cancer cell line/ RENCA	Single wall carbon na- nohorns	50-100 nm	Hyperthermia /SWNHs could be used in clinical ap- plications to treat superficial tumors	[30]
14	670 nm	Pulsed	25 micro watt	MDA-MB231 human breast cancer cells / Athymic nude mice	CPT-HGC	254 nm 288 nm	Tumor apoptosis	[31]
15	671 nm	CW	~2 W/ cm <sup>2</sup> for 3 min.	MDA-MB-435	Photosensitizer-Load- ed Gold Vesicles	50-150 nm	Photoablation	[32]
16	671 nm	CW	200mW	HeLa cells	Silica coated Gold na- norods	Aspect Ratio 3±0.2 /3 nm silica coating	Hyperthermia induced ap- optosis	[33]
17	671 nm	CW	2W/ cm <sup>2</sup>	MDA-MB-435 tumor bearing mice,A549	GNS-PEG-Ce /Gold nanostars	78.0 ± 2.9 nm	Photothermal ablation	[34]
18	690 nm	CW	38 W/ cm <sup>2</sup>		Gold nanoparticles		Necrosis	[35]
19	671 nm	-	~2 W/ cm <sup>2</sup> for 1 min	MDA-MB-435	Photosensitizer-Con- jugated Silica-Coated Gold Nanoclusters / AuNCs@SiO2-Ce6	-	Photothermal ablation tem- perature increased up to 43 C causes protein denatura- tion and necrosis of the cells through lysis or rupture of cell membranes.	[36]
20	671 nm (di- ode-pumped solid-state la- ser system)	-	90 J/ cm <sup>2</sup> , 75 mW/ cm <sup>2</sup> 2-8mW/ cm <sup>2</sup>	e 4T1 murine Breast cancer cell line	Nano-Graphene /GO- PEG-HPPH	< 50 nm	Endocytosis: Mechanism of cytotoxicity was through photo dynamic action PDT with GO-PEG-HPPH significantly decreased the oxygen saturation of tumors, which can be evaluated by PAI.	[37]
21	671 nm	pulsed	220 mW/ cm <sup>2</sup>	HT-29 tumor- bearing mice	HGC-Ce6 and GC-Ce6 /Mice	300 to 350 nm	Ce6s in the HGC-Ce6 can ge- nerate singlet oxygen at target cellular organelles such as mitochondria showed severe phototoxicity	[38]
22	690 nm		1.84 mW cm <sup>-1</sup> for 10 min.	HeLa cells	Phthalocyanine-nano- particle conjugate	2-4 nm	The cells show the presence of blebs and vacuoles and are indicative of cell mortality possibly induced by apopto- sis.Further evidence of apop- tosis was provided through the bioluminescent assay detection of caspase 3/7.	[39]
23	690 nm	CW	38 W/ cm <sup>2</sup>	HER2 positive SKOV3, HER2 negative CHO	Branched gold nano- particles bind to HER2 antigen	60 nm	Photothermal therapy by hyperthermia induced cell death.	[40]
24	730 to 870 nm /NIR FS Laser	Ultra fast Pulsed laser	100 mJ cm <sup>2</sup> / 27.8 W cm <sup>2</sup>	HeLa cells	Transferrin conjugated Gold nanorods.	aspect ratio of 4.0	Necrosis	[41]



25	775 nm	Pulsed	1 to 20 W/ cm <sup>2</sup>	HeLa cells	SiNc4 onto MFG via pep stacking to yield MFGeSiNc4		Apoptosis by Singlet oxygen/ Combined PDT and PTT	[42]
26	785 nm	-	2.4 W/ cm <sup>2</sup>	Her 2/SKBR3	Au/Magnetic	670 nm	laser ablation into heat	[43]
27	785 nm	CW OEM Laser	1.5 W/ cm <sup>2</sup>	MDA-MB SK-BR-3& HER2/c-erb-2/ Neu	Gold Nano Popcorn attached SWCNT	-	Photothermal ablation	[44]
28	790 nm	Pulsed	85.5 pJ / pulse 300 s	Hela Cells	Hypericin loaded Gold Nanocages	45 nm	Photothermal ablation and necrosis /PDT and PTT	[45]
29	808 nm (diode laser)	CW	8.5 × 10 <sup>4</sup> W/m <sup>2</sup>	CCRF-CEM cells NB4 cells, HeLa cells	Aptamer-Conjugated Au-Ag Nanorods	14 nm width, 53 nm length	Mechanical and acoustic damage to the membranes	[46]
30	808 nm	CW	0.5 W/ cm <sup>2</sup>	U87MG with EGFR human glioblastoma cell / tumor-bearing mice	PEG coated Gold nanocages	48±3.5	Photothermal therapy with cogulative necrosis	[47]
31	808 nm	CW	2mJ/ cm <sup>2</sup> /pulse	<i>in vivo</i> /rat	Nano-rGO	0.8-1.2 nm	Photothermal ablation/ These data indicated that the apoptosis and death of cancer cell caused by the PT effect mediated by nano-rGO	[48]
32	808 nm	CW/fs	4 W/ cm <sup>2</sup>	<i>in vivo</i> /Mice	Gold Nanorods	3.8 to 6.7	Photothermal	[49]
33	808 nm	CW	5W/1.2W	Human brain astrocytoma cells (1321N1; ECACC 86030402)	Gold nanorods		Photothermal ablation	[50]
34	808 nm	CW	0.9-1.1 W/ cm <sup>2</sup> w	HSC-3 human squamous carcinoma cells	PEGlated Gold nanorods	4.0 aspect ratio	Hyperthermia indicate membrane blebbing	[51]
35	808 nm	CW	2 W cm <sup>2</sup>	H22 tumor in mice	Bismuth selenide Bi <sub>2</sub> Se <sub>3</sub> nanoplates	90 nm	Hyperthermia	[52]
36	808 nm	CW	1.4 W/ cm <sup>2</sup>	PC3 human prostate cancer cell line and S180 mouse ascites tumor cells	SWNT- NGR-DTX	182.8 ± 2.8 nm	Photo thermal ablation	[53]
37	808 nm		15.3 W/ cm <sup>2</sup>	Human Saos-2 osteoblasts, murine L929 fibroblasts, murine RAW-264.7 macrophages and murine MC3T3-E1 pre-osteoblasts	NANO-GO		Microbubbling can be induced by irradiation	[54]
38	800 nm	CW	80 W/ cm <sup>2</sup>	Human prostate carcinoma cells (PC3, ATCC; Manassas, VA)	Gold / Gold Sulfide Nanoparticles	35-55 nm	Photothermal ablation	[55]
39	808nm	CW	0.6 W/ cm <sup>2</sup>	BALB/c miced with 4T1 tumor	Carbon Nanotubes/ AuNR	140 nm	Highly effective tumor elimination with SWNTs was achieved at 10 times lower injected doses and lower irradiation powers than for AuNRs. Hyperthermia	[56]

40	808 nm	-	1 W/ cm <sup>2</sup>	Murine breast cancer 4T1 and human embryonic kidney 293T/ Balb/ c mice	Organic PEDOT: PSS-PEG. -poly (3,4- ethylenedioxythiophene); poly (4-styrene- sulfonate) (PEDOT:PSS),	80 nm	Photothermal ablation of cancer.	[57]
41	808 nm	CW	2 W/ cm <sup>2</sup>	Mice/EMT6 cells	Doxorubicin-loaded PEGylated nanographene oxide	100 nm	Photothermal ablation	[58]
42	808 nm	CW	1.5 W cm <sup>2</sup>	Nude mice bearing HT-29 tumors/Hela Cells	Au NPs coated with Prussian blue (PB)	18 nm	Localized tumor photothermal effect	[59]
43	808 nm	-	2 W/ cm <sup>2</sup>	balb/c mice with 4T1 r tumors, nude mice bearing KB tumors, and U87MG tumors	NGS- PEG	30 nm	Photothermal	[60]
44	808 nm	CW	-	Human prostate cancer cells (PC-3)	Silica and Gold Nanoparticles		Hyperthermia	[61]
45	808 nm		35 W/ cm <sup>2</sup>	MCF-7 tumor-bearing BALB/c nude mouse	Targeting Gold Nanoshells on Silica Nanorattles	158 nm to 185 nm	Thermal ablation	[62]
46	808 nm		1 W/ cm <sup>2</sup>	KB cells	Single-layer MoS <sub>2</sub> nanosheets			[63]
47	808 nm	CW	24 W/ cm <sup>2</sup>	HeLa cells,HEK293	Copper sulfide nanoparticles	3 nm	Photothermal ablation	[64]
48	670 nm/ 808 nm		1.5 W/ cm <sup>2</sup>	Murine colon cancer cell lines (CT-26)	Porous silicon nanoparticles	80-220 nm	The cell deaths were mostly due to necrosis but partly due to late apoptosis.	[65]
49	800 nm	CW	20 W/ cm <sup>2</sup>	Human prostate cancer cell line PC3-PSMA	Gold Nanorods		Hyperthermia	[66]
50	800 nm	CW	40,60,80, 20, 160,200 mW	HOC,HaCat,HSC	Anti-EGFR/Au Nanorod Conjugates.	aspect Ratio 3.9	Photothermal therapy	[67]
51	800 nm	Pulsed	~ 30 mW 18 mJ/ cm <sup>2</sup>	EMT-6	FePt NP	12+1 nm	Photothermolysis	[68]
52	800 nm		7 W	Human prostate carcinoma cells/ (PC3)	Gold / gold sulfide nanoparticles	35-55 nm	Photothermal Ablation	[69]
53	800 nm	Pulsed	4.77 W/ cm <sup>2</sup> / 5 min	SK-BR-3 cells	Immuno gold nanocages	65 ± 7 nm	Photothermal effect	[70]
54	810 nm	CW	8.16 W/ cm <sup>2</sup>	Cal-27 (Human oral squamous cell carcinoma cell line, CRL-2095, ATCC)	Rose-bengal-conjugated gold nanorods	13.2 nm and 52.4 nm,	Photodynamic and Photothermal.It has been reported that apoptosis may be the preferred mechanism of cell death induced by RB mediated PDT	[71]
55	820 nm	Pulsed	15-40 mJ/ cm <sup>2</sup>	HN31,co-cultured with normal epithelial NOM9 cells	Plasmonic nanobubbles	13.2 nm and 52` 4 nm,	Plasmonic nanobubble-enhanced endosomal escape	[72]
56	820 nm	Pulsed	40 mJ cm <sup>2</sup>	OCSCC	Chemotherapy with PNBs	-	Photodynamic and Photothermal	[73]
57	820 nm	Pulsed	15 W/ cm <sup>2</sup>	A431, MCF 7	Drug-Loaded Polymer Gold Nanoshells	-	Localized photothermal treatment by NIR laser illumination.	[74]
58	980 nm	-	0.51 W/ cm <sup>2</sup>	Ex vivo	Cu9S5 NCs (Hydrophilic Cu9S5 Nanocrystals)	-	Photothermal ablation	[75]

59	980nm	-	1 W cm <sup>2</sup> for 10 min	EMT6 cells	Single-Walled Carbon Nanotubes	0.81 nm	Mitochondria targeting	[76]
60	980 nm	CW	0.5 W/cm <sup>2</sup>	<i>In vivo</i> MC 540	NaYe4:YbEr		The combination of PDT with chemotherapy also possesses excellent drug loading capability and anticancer efficiency	[77]
61	800 nm	CW	80 mJ cm <sup>-2</sup>	MDA-MB-231 breast cancer cells	Gold Nanoparticles	30-40 nm		[78]
62	550 nm	300 W halogen lamp	25 mW cm <sup>-2</sup> /22.5 J cm <sup>-2</sup>	non-pigmented human melanoma A375 and pigmented mouse melanoma (B16F10) cell lines	Pc4 in Silica Nanoparticles	25-30 nm	Apoptosis by singlet oxygen (Type II). /Pc4 in silica nanoparticles generated photo-induced singlet oxygen Pc4SNP photodamaged melanoma cells primarily through apoptosis	[79]
63	690 nm	Short single laser pulses	-	C4-2B	Gold Nanoparticles conjugated with C225 anti-EGFR antibodies	60 nm	Plasmonic nanobubbles produce photoablation. The fast expansion of the vapor bubble has a localized mechanical and non-thermal impact on the environment	[80]
64	800 nm	Pulsed	25mW/0.2 mW	HeLa cells	PEG-NRs and PEG-Tf-NRs.		Membrane blebbing	[81]
65	780 nm	-	24 and 48 W cm <sup>-2</sup>	A549 cells	Mesoporous silica coated gold nanrod-sAu@SiO <sub>2</sub>	30 nm	Hyperthermal cancer therapy	[82]
66	White light source/ band pass filter (400-700 nm)	-	150 mW/cm <sup>2</sup> white light, 1-80 J/cm <sup>2</sup>	J774, LLC and CT26	Superparamagnetic iron oxide nanoparticles	-	Monocationic fullerene is a highly effective PS for killing cancer cells by rapid apoptosis	[83]

nm in 32 groups, 980 nm in 3 research groups were listed in table 1. In more than 50 % of articles, 775 nm-820 nm NIR laser is used. 21 % work uses 640-690 nm red lasers. Few research groups use 532 nm green lasers. Red laser and NIR laser were commonly used due to the tissue transparency in therapeutic window region (650 nm-1100 nm). Laser with continuous wave and pulsed mode was used in photo nano therapy. 42% continuous mode and 20 % pulsed laser were used. In ~35% research articles the mode of laser is not mentioned (figure 3). In photo nano therapy laser power ranging from 0.5 W to 1 W were used. The fluence varies and the mechanism of cell death depends on the mode and fluence rate of laser (Table 1)

The effect of phototherapy was demonstrated by low power laser irradiation at 808 nm with 0.8 W/cm<sup>2</sup> to induce efficient photodynamic effect from Indo cyanine green (ICG) dye. The photothermal effect from the ICG and Single wall carbon nanotubes (SWCNTs) rapidly raised tumor temperature to ~55 °C. The temperature rise leads to tumor growth inhibition, tumor cell death and necrosis [19]. MDA-MB-231 cells, upon exposure to NIR laser of 808 nm and dual drugs (doxorubicin and irinotecan)-loaded GO (grapheme oxide), activates the intrinsic apoptosis pathway and cell ablation [84]. When tumor necrosis factor-alpha coated gold nanospheres (Au-TNF) irradiated with 532 nm and 690 nm, nonlinear photothermal and photoablation phenomena appeared. [86]. Irradiation with external near-infrared laser (NIR) with PS in mitochondria caused serious mitochondrial matrix swelling for the activated upconversion-

based photodynamic therapy (UC-PDT). In UC -PDT mobilization of cytochrome c (cyt c) was amplified in response to the increased mitochondrial reactive oxygen species (ROS), causes apoptosis. [88]. For micrometer-sized melanin particles, the temperature for bubble initiation has been estimated to be 140-150°C. Through these studies, NIR laser were used in PNT, ends up with different cell death mechanism against different nanoparticles. In table (1), cell mechanisms involved in PNT with Visible-NIR laser irradiation were addressed in detail.

Laser mechanism could be better understood with gold nanoparticles. In this review 46% of researchers use different form of gold nanoparticles and gold nano conjugates for photo nano therapy. Gold nanoparticles were preferred due to biocompatibility, absorption in visible and NIR region and easy conjugation to biomolecules. Rests of the nanoparticles included in this review are carbon nanotubes (CNT), iron oxide nanoparticles (FeO<sub>2</sub>), silica nanoparticles, porphyrin and chemical conjugates. The sizes of nanoparticles were ranging from 0.8 nm to 100 nm were (Table 1). Conjugates of nanoparticles more than 100 nm were also studied by few research groups [33].

In photonanotherapy the cell death was quantified and very few research articles only deals with cellular mechanism. Instead, GNPs were worked out in detail and the role of laser in nano medicine can better understand with GNPs. GNPs Surface Plasmon Resonance is tunable from 520-1200 nm based on their size and shape. GNPs also release scattering signals, which can be used for imaging. Gold nanorods with 480 nm excitation,



emits fluorescence around 550-600 nm and gold nano clusters with 230 nm laser excitation give fluorescence at 440 nm. GNPs excited with 785 nm red laser gives surface enhanced Raman Scattering (SERS) signals (Figure 4). In this review, nearly 50% of researchers use GNPs in various forms such as of gold nano spheres (Vis), nanorods (NIR), gold nanoshells, and gold nanocages etc as photosensitizers. The surface electrons create modified response in GNP when hits with laser of different wavelength and power, shown in figure (4). Gold nano spheres when exposed to high power II harmonic 532 nm Nd:YAG laser releases thermal energy and produce cavitation bubble around the nanoparticle [11]. The same gold nano particle creates hyperthermia and delayed apoptosis with diode low power Nd :YLF laser of 532 nm [89]. The cellular responses by GNPs mediated photo nano therapy are photothermia [18-21,53,54,73,75], hyperthermia [39,56,73], apoptosis [33], membrane blebbing, photo ablation [32,40,46,48,55,60,67,74], micro bubble formation [22,47], necrosis [35,41,48,51] and cell vaporization, listed in table 1. Photothermia leads to increase in temperature in target cell causes cell death and the thermal increase not limited in hyperthermia range.

Pitsillides et al., reported, the photothermal therapy of lymphocytes using GNP immune conjugates coupled with a nanosecond Nd: YAG- pulsed laser II harmonic at 532 nm. Nd: YAG laser induces solvent bubbles around the particles that imposed enough mechanical stress to cause cell destruction [11]. Around the same period, Zharov et al. studied the factors that affect the killing energy, such as the number of pulses. Pitsillides articulate size as well as the dynamics of the thermal events around GNPs were important to understand the killing efficiency and mechanisms involved [16]. Studies by El-Sayed and colleagues demonstrated selective photo thermal therapy in cancer cells by using 40 nm gold nanoparticles conjugated to anti- EGFR antibodies exposed to a visible cw Argon ion laser.

In PPT, malignant cells required less than half the laser energy to be killed as compared with the benign cells. In addition, no photothermal destruction was observed for any of the cell types without nanoparticle labeling, even at four times the energy required to kill the malignant cells labeled with anti-EGFR/Au conjugates [62]. Zharov et al investigated bubble formation from nanoparticles. In the work 40-nm-diameter GNS distributed on a cell, 30 pulses of 0.5 J/cm<sup>2</sup> or one pulse of 2 J/cm<sup>2</sup> resulted in death of all cells. Alternatively, with cluster formations, cell damage occurs after 100 laser pulses at 80 mJ/cm<sup>2</sup>[16]. Peng et al., focused on the effects of laser irradiation on particle size and peak absorption wavelength. Peng et al showed that using a Nd:YAG laser and 21-nm spherical gold nanoparticles, the irradiation causes the particles to fragment to an average diameter of 4.9 nm, changing the peak absorption wavelengths. GNPs subjected to irradiation using a nanosecond Nd: YAG laser source of 7 ns pulse, 532 nm wavelength adjusted to the same total dose as in the case of CW laser irradiation set of experiments (30 mJ/cm<sup>2</sup>/ pulse, 100 pulses per minute). In the work, an 7-fold increase of chemical quenching was observed, indicative of a significantly higher rate of <sup>1</sup>O<sub>2</sub> production [19]. The evidence of producing <sup>1</sup>O<sub>2</sub> by irradiating GNPs were found with CW and pulsed laser sources. Two distinct pathways of <sup>1</sup>O<sub>2</sub> production are involved during GNPs irradiation: i) A plasmon activated pathway that proceeds by the interactions of plasmons and hot electrons with molecular oxygen; ii) An indirect photo thermal pathway more pronounced in the case of GNPs irradiation with pulsed laser sources that induces extreme heat development leading to particle fragmentation and increased thermionic electron emission. As a result, <sup>1</sup>O<sub>2</sub> and ROS generation is more efficient during irradiation with pulsed laser sources compared to the irradiation with CW lasers. Pulsed laser contributes significantly to the overall cancer cell death rates during photo thermal laser treatment [19].

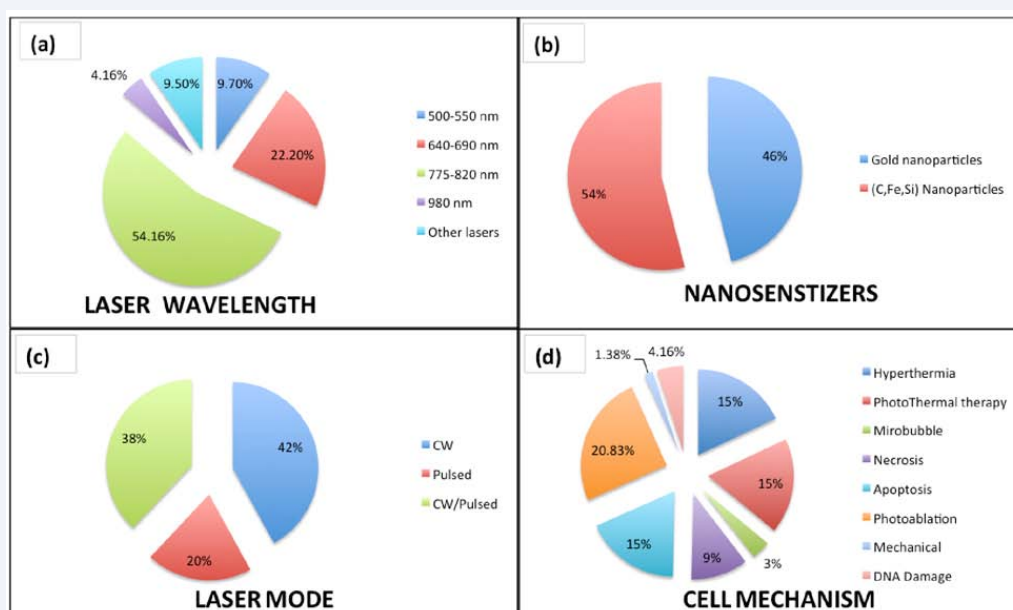


Figure 3 Statistical distribution of laser, nanoparticle parameters and cell mechanism.

GNPs are able to quickly convert the absorbed energy into heat energy in the picosecond time domain, making them excellent agents for hyperthermic cancer treatment [90]. In microbubble formation, as the bubble grows, the vapor cools and condenses. The bubble cannot sustain itself and implodes [11]. The lifetime of the bubble is a function of its size at maximal expansion [85]. Huang et al trigger apoptosis of cancer cells by manipulating the energy fluence. When the laser power density is high, GNPs fragmented results in localized mechanical shock to the cell membrane causing membrane perforation. At a low power, when the energy fluence is high enough, the heat produced from gold

nanorods can also burn the cell membrane. These two effects will compromise the integrity and cause leaking of cell membrane, leading to rapid cell death by necrosis [41]. A gold nanoparticle creates responses in cells by all the possible mechanism when hit with different wavelength, mode and fluence of laser. When we deal with the dark side of gold, GNPs were alone produce toxicity in cells. Butterworth et al showed that millimolar concentrations of 1.9 nm gold particles decreased cell viability by 30% in bovine aortic endothelial cells [90]. A recent in vivo study, Cho et al showed that 13 nm PEG-coated gold nanoparticles had significant in vivo toxicity causing acute inflammation and apoptosis in the

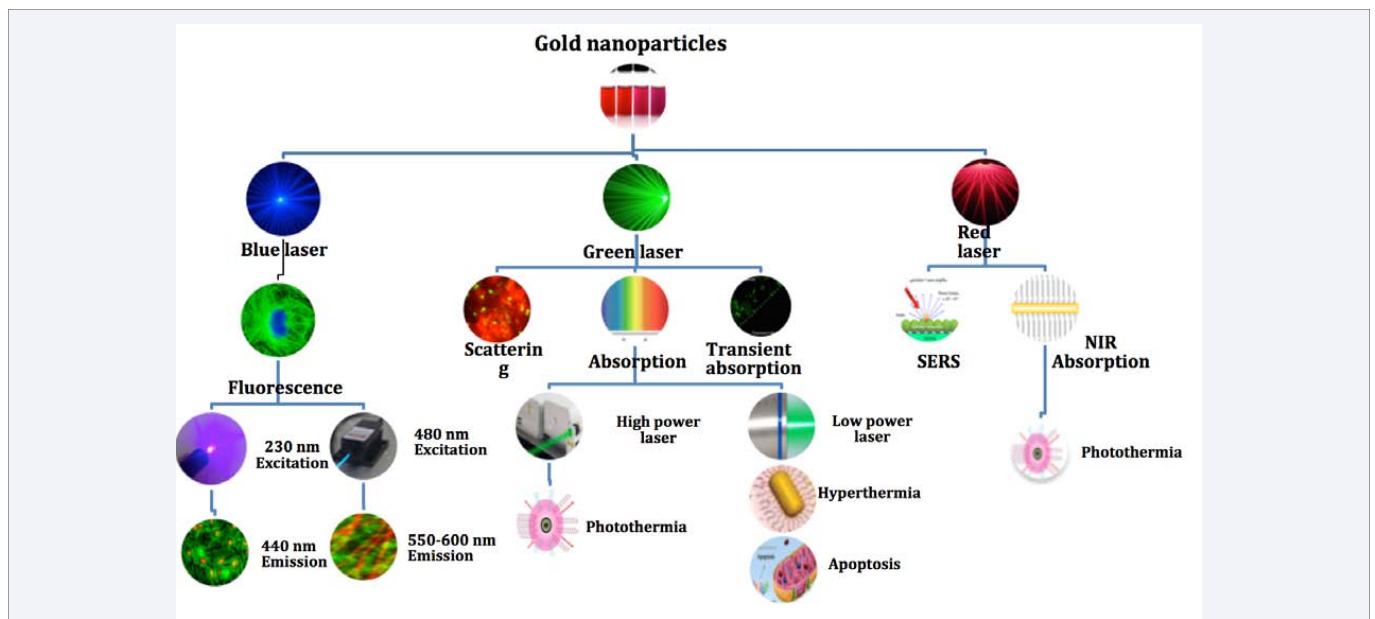


Figure 4 Optical and cellular response by gold nanoparticles while hits with range of wavelength.

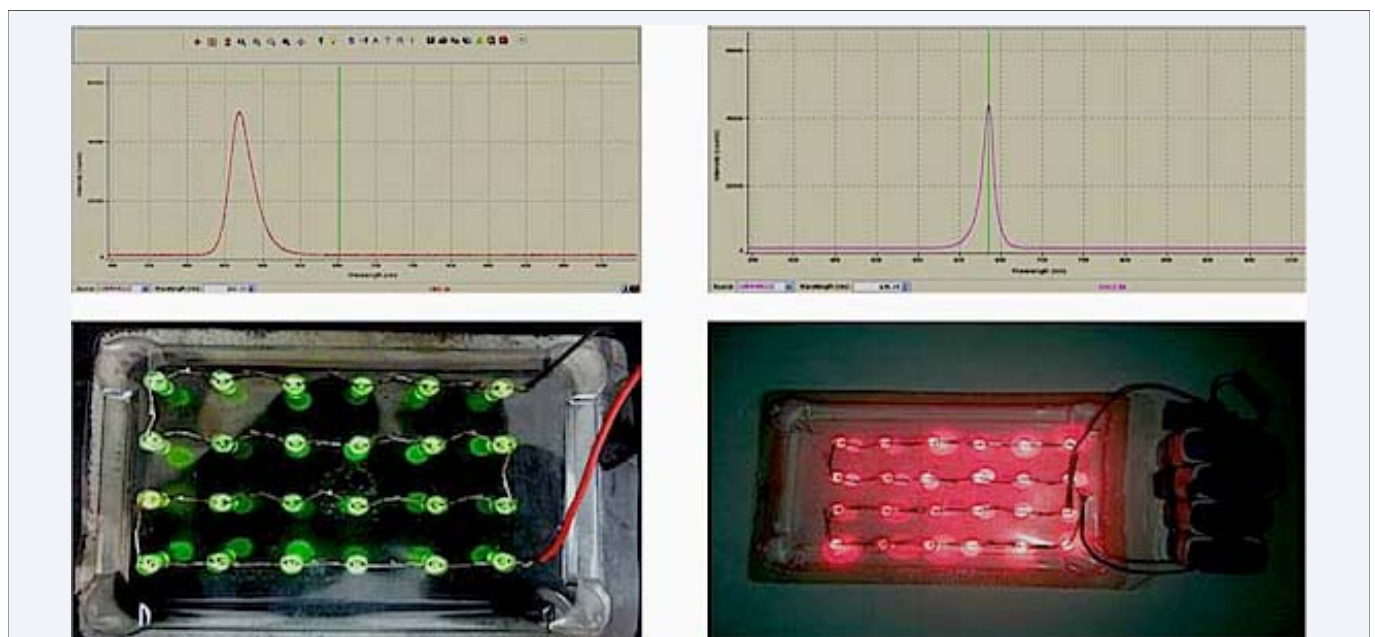


Figure 5 Portable green and red LED designed for 96 well plate. Wavelength spectra of green LED and red LED (top).

livers of BALB/ c mice [90]. Conversely, Connor et al failed to show acute toxicity for cysteine and citrate capped 4 nm particles and 18 nm cetyl trimethyl ammonium bromide (CTAB) particles [90].

### CW/Pulsed Laser?

The comparison made between CW and femtosecond pulsed laser by Tong et al., confirms that short-pulsed laser was more effective than CW laser [55]. The responses from cells as a function of the length of time through the irradiation area were revealed by Hong et al [60]. At a low laser pulse energy photo thermal responses were observed without cell damage; a fast-rising initial peak due to quick heating of the cell through absorption by cellular chromophores and a lower exponential tail corresponding to cell cooling as a whole through heat diffusion into the surrounding solution. Femtosecond laser micro-surgery (FLMS) has emerged as a superior technique for ablation of cells and subcellular structures radiation therapy. In FLMS, laser absorption is confined to the focal volume by nonlinear interaction. This technique has been used clinically for surgery since 2003. The combination of gold nanoparticles with FLMS can lead to the development of less invasive hyperthermia treatments [71]. Folate-GNRs showed the stronger thermolysis effect by fs-pulsed laser irradiation than CW laser due to the increased ultrafast electron dynamics involved in plasmon-mediated heating [55]. Major advantage of photo nano medicine is surrounding cells are not affected as in other modes of therapy. Designing fibre coupled laser and selecting wide laser source for nanoparticle helps photo nano therapy to advanced levels for invasive and non-invasive treatment for cancer. Lasers are advantageous over other irradiation sources since the noninvasiveness and availability in selected wavelengths minimize laser application in cancer therapy. As an alternate, light-emitting diodes (LEDs)—a monochromatic noncoherent low-power light source may be used. LEDs along with GNP have its own merits that provide therapeutic benefits of PPT when compared to lasers. Prof. Tina Karu states that the coherence of light is of no importance in low-power laser clinical effects [90]. Light Emitting Diode (LED) found to be an alternate for LASER in PPT. A comparison between LED and Laser of 530 nm and 532 nm wavelengths were used as irradiation source in normal cell lines with same fluency. Cells incubated with GNP and irradiated with LED and laser (Figure 5). Apoptotic bodies were developed in both cases and the surrounding cells were intact [90]. Fibre coupled LEDs can be used for in vivo applications. In superficial tissues multiple LED can be used simultaneously and design the source based on the application requirement. LED is monochromatic non-coherent light source and can easily fiber coupled to reach the deep-seated tissues and was available in all wavelength range.

By the power and precision, lasers are well suited for cancer surgery and medicine; by portable, easy to make fibre coupled devices, economic, wavelength independent properties, LED also seed attention as an irradiation source. When cancer surgeons start to use lasers, as well as when lasers become smaller and cheaper and technology improves to reach deep-seated cancer, lasers may become regular practice for cancer treatment. Thorough knowledge in cellular mechanism helps to brighten cancer therapeutics with non ionizing radiation.

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