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Breakthroughs of using Photodynamic Therapy and Gold Nanoparticles in Cancer Treatment

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***Abstract*— The term "cancer" covers more than a hundred diseases that assign one trait: the abandoned growth of abnormal cells that abolish healthy tissues and have the potential to spread outside its site of origin. When a malignant tumor originates in the breast, it is called breast cancer. Gold nano particles display potential for both the imaging and cure of breast cancer. From a logistical standpoint, most breast tumors arise near the skin's surface, where they may possibly be extracted and handled despite the NIR laser's minimal tissue penetration.Photodynamic therapy is a fairly new treatment option for both cancer and non-cancer diseases that involves the activation of certain dyes with light in the existence of molecular oxygen (photosensitizers) that the target tissue has absorbed in a very selective manner. The combination of hyperthermia and photoelectric dose improvement of radiation therapy could be effectively treat superficial positioned inflammatory breast cancersorrecurrenceinthepost-mastectomychestwall.Inthis review paper, the novel work in photothermal therapy is debated, as well as the combined effects of gold nanoparticles and photothermal heating on breast cancer cells are studied in details.**

***Keywords*— gold nanoparticles, PDT, breast cancer, laser**

I. Introduction

T Photodynamic therapy (PDT) is a two-stage therapy that iindicates light energy with a drug (photo sensitizer) intended to damage pre cancer thousand cancerous cells after light activation of specific dyes (photo sensitizers) that have been absorbed by the target tissue in the existence of molecular oxygen. Photosensitizers are molecules that engross energy from particular wavelengths of light and then use that energy to persuade non-absorbing molecules to respond. For the treatment to work, all three components (photosensitizer, light, and oxygen) must be present. OscarRaab's experiments on the impact of light and dyes on Paramecia in 1900 gave birth to the idea of PDT[1].Lipson and Schwartz at the Mayo Clinic discovered that injecting rudimentary hematoporphyrin preparations resulted in fluorescence of neoplastic lesions that could be seen during surgery, kicking off the new period of PDT.Since then,wide spread work has been done on how the process works, how to maximize efficacy using animal models, and how to finest treat human tumors [2]. Source of light, transportation, and distribution after the invention of the laser, which allowed the development ofmonochromatic light that could be easily coupled into optical fibres, PDT became widely used.

II. Oxygen and oxygenation strategies for PDT

The yield of singlet oxygen is most likely linked to the efficacy of PDT with photosensitizers that localize in tumor tissue (1O2) in the tumor [3]. The yield of $^1O_2$, in turn, depending on the tissue's oxygen concentration [4]. Some tumors may have oxygen concentrations that are very low for PDT to be effective [5]. Both the supply of blood and the absorption of oxygen are essential regulate the amount of free oxygen attainable in a tissue. PDT is also very immune to completely hypoxic cells. Breathing a perfluorochemical emulsion (5% CO_2,95% O_2), may improve tumor oxygenation, which may alter the outcome of PDT in some circumstances. The PDT reaction mechanism itself may consume oxygen at a high enough rate to prevent further PDT effects [6], [7]. It has been suggested that hyperbaric oxygen could improve the PDT result [8]. A recent research in Wistar rats using the Walker 256 tumor model confirmed the enhancement of PDT effects under hyperbaric hyperoxia [9]. Histological parts were measured after PDT therapy of tumors at 3 atmospheres (atm) and controls at 1 atm to determine the enlarged depth of tumor damage. Ex vivo morphometric analysis revealed a complete loss of cell viability in treated tissue as compared to control tissue.More experimental research in this area is needed. Another easy way to overcome oxygen diffusion limitations is to fractionate light transmission (e.g., 30 seconds on, 30 seconds off) or to lower the fluence rate. Oxygen diffusion can compete with oxygen consumption in these protocols, resulting in a better tumor response [10], [11].

III. Nanoparticles in cancer treatment

Nanoparticles are most broadly used in the biomedical fields for analysis and cure of cancer. Treatment of tumors surrounded by vital tissues is problematic and there is a probability that tumor limits remain unclear. On the contrary, cutting healthy tissues may lead to intolerable beauty and medical results. Application of nanoparticles offers a high

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degree of precision. On the other side near infrared (NIR) radiation is an interesting energy source as human blood and body tissues have the lowest absorption in this wavelength, thus profounder tissues can be extended [12]. The unique aspects of lasers such as photo-thermal properties and the extremely small size of nanoparticles (which generates new physical effects that are mainly a result of power of the quantum properties in contrast to classical properties), provide an interesting combined healing effect. Thermal therapy procures a fast recovery, shorter hospital stay, less complications and is easy to perform [13]. Nanoparticles derived in a variety of shapes and sizes, each with its own set of properties and applications, such as nanorings, nanoshells, nanorods, nanopores, and nanowires. Depending on the peak absorption of nanoparticles, various lasers are employed. For example researchers have examined NIR-tunable nanostructures (nanoshells,[14], [15] nanorods,[16] and nanoclusters,[13], [17]etc) for photo-thermal performance[18]. In fact, in nanoparticles that have been synthesised to date, the most absorption has been found in the wavelength range of 600-1200 nm (laser diode). Nanoparticles with optimum absorption in other wavelengths will be developed in the future. Liver, spleen and kidneys are sites that are most stimulated by nanoparticles [19]. The usage of gold nanoparticles modified with thiol monolayers such as tiopronin is motivated by morbidity and renal complications. [20]. Mutable toxicity of nanoparticles is attained through diverse size and the material which coats them.

IV. Gold Nano particles and Nanotechnology

Gold nanoparticles are being studied as drug carriers, photothermal agents, contrast agents, and radiosensitizers as well as other applications in cancer therapy (Fig. 1) [21]. The “bottom-up” strategy in molecular electronics and biosensor technology often uses biohybrid complexes where biological molecules, DNA and peptides in particular, act as templates. It is therefore of present interest to gather the DNA molecule directly on gold nanoparticles. In addition, the mechanism of interaction between the DNA and gold is by itself a vital issue, both theoretically and experimentally. Recent experimental studies showed that DNA bases, adenine (A), thymine (T), guanine (G), and cytosine (C) interact with Au surfaces in a specific and sequence-dependent manner. The relative binding affinities of these nucleobases for adsorption on polycrystalline Au films obey the following order: A > C G > T (see, e.g., Kryachko (2009)) [22], [23].

V. Tissue distribution of laser-ablated dextran-coated AuNP (AuNPd)

Pharmacokinetic parameters show a quick clearance of laser-ablated dextran-coated AuNP (AuNPd) from the bloodstream. To regulate the distribution of AuNPd in tissues, three groups of six mice were managed with 1 mg/kg of AuNPd and sacrificed at diverse times after injection: 24 h, 7 and 14 days. The control group was injected with vehicle alone and sacrificed at day 14. Gold concentration in various tissues, including liver, spleen, kidney, heart, lung and brain, was measured by ICP-MS and expressed as ng/mg organ. Twenty-four hours after injection, spleen and liver were special sites for gold gathering with 8.78 ± 4.33 ng/mg and 6.36 ± 3.37 ng/ mg (Fig. 2), separately. However, considering size of the organs, AuNPd accumulated mostly in liver, in which Au concentration was more than 35% of the injected dose after 24 h and more than 50% after one and two weeks (Table 1).

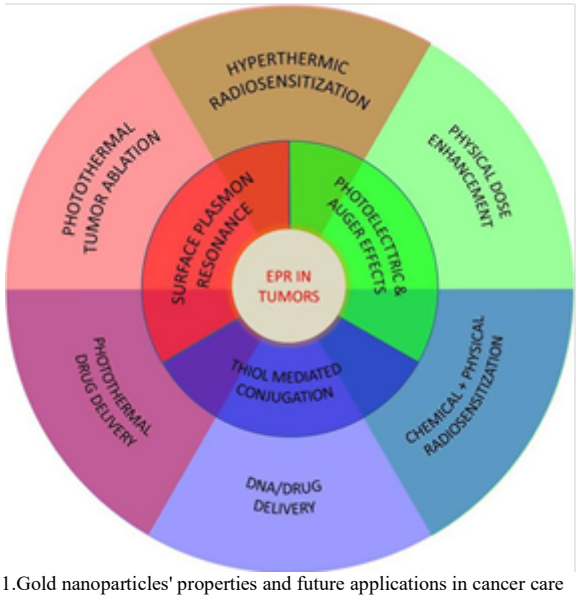


Fig.1.Gold nanoparticles' properties and future applications in cancer care The nanoparticles are trapped within the tumour by the enhanced permeability and retention (EPR) effect, where they can be stimulated with light (surface plasmon resonance), used to increase the consequence of radiation (secondary electrons), or delivered drugs/DNA. In cancer care, either or a combination of these techniques can be beneficial.

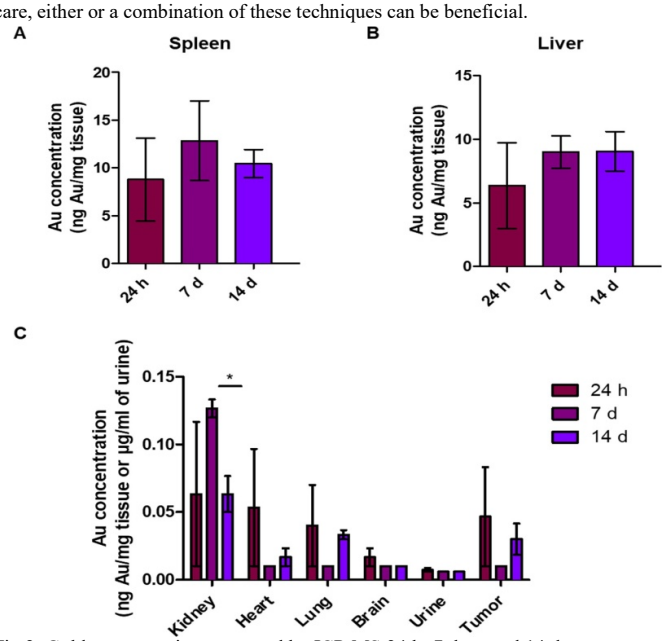


Fig.2. Gold concentration measured by ICP-MS 24 h, 7 days and 14 days after a single injection of AuNPd (1 mg/kg). (n = 3, data are mean ± SEM).

TABLEI. GOLD CONCENTRATION EXPRESSED IN PERCENTAGE OF INJECTED DOSE IN SPLEEN, LIVER AND KIDNEYS

Organ	Time post-injection	Au quantity per organ (% of injected dose)	
		Mean	SEM
Spleen	24 h	4.74	2.34
	7 days	6.93	2.25
	14 days	5.65	0.79
Liver	24 h	35.36	18.77
	7 days	50.07	7.05
	14 days	50.42	8.61
Kidney	24 h	0.12	0.10
	7 days	0.23	0.01
	14 days	0.12	0.02

In other organs and in tumor, gold concentrations were much lower with less than 0.15 ng/ mg of tissue at 14 days. The lowest concentration was found in the brain with less than 0.03 ng/mg (Fig. 3). Moreover, no statistical difference was found between gold concentrations at different time point in lungs, heart, brain and urine. In addition, since less than 0.1 percent of the injected dose was contained in urine, AuNPd were not cleared by the kidney.All together, their results indicate that AuNPd collected mostly in the liver, without obvious decrease for 14 days [24].

VI. FUTURE PERSPECTIVES FOR BREAST CANCER TREATMENT

Breast cancer is the most common cancer in women around the world, accounting for about 1.7 million new cases in 2012, or about 25% of all cancers in women. Incidence rates vary widely across the world, from 27 per 100,000 in Middle Africa and Eastern Asia to 92 per 100,000 in Northern America (Fig. 4). Breast cancer can attack nearby breast tissue, spread to the lymph nodes in the armpits and toother sites of the body, such as the lungs, bones, liver and brain. It can impair the role of the affected organs and, potentially, the life of the patient.

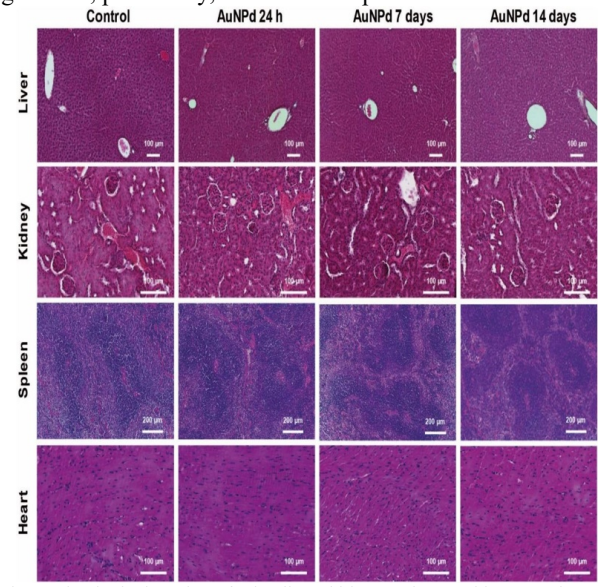
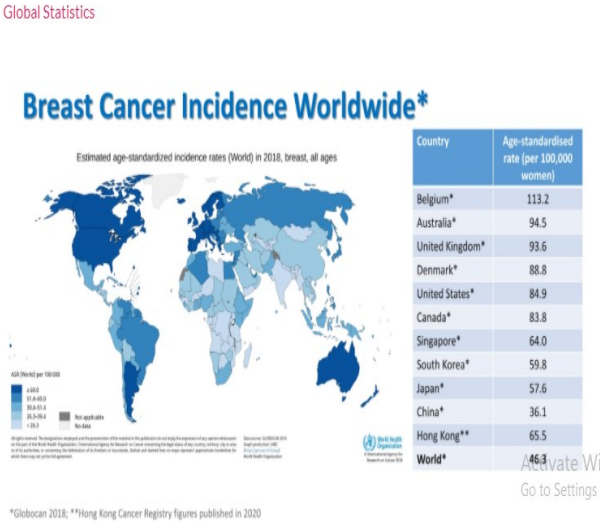


Fig. 3 Histological section of mice liver, kidney, spleen and heart, 24 h, 7 and 14 days after intravenous administration of AuNPd (1 mg/kg) compared to the control groupadministered with vehicle alone.

The survival rate of breast cancer is very high if it is spotted at an early stage. Early revealing can also save onerous medical costs and decrease the need for extensive treatment(s) and the related negative physical and psychological impacts. Some studies have shown that only 0.7–5% of an intravenously administered dose of gold nanoparticles accumulates in tumor tissue, suggesting that intratumoral injection could be effective for some superficially located tumors[25]–[27]. Nanoparticle management could be beneficial not only for imaging or curative therapy of early-stage cancer, but also for palliative local regulation of more advanced breast tumors.



Country	Age-standardised rate (per 100,000 women)
Belgium*	113.2
Australia*	94.5
United Kingdom*	93.6
Denmark*	88.8
United States*	84.9
Canada*	83.8
Singapore*	64.0
South Korea*	59.8
Japan*	57.6
China*	36.1
Hong Kong**	65.5
World*	46.3

Fig.4. Breast Cancer Incidence Worldwide

From an imaging standpoint, contrast offered by gold (a higher atomic number element than calcium) would be even more marked on mammography. Intraoperative visualisation of surgical resection margins based on tumor-specific nanoparticle uptake and non-contact large-field gold nanoparticle imaging techniques can also help surgeons ensure resection margins. The problem is figuring out how to concentrate gold nanoparticles inside tumour cells rather than benign breast tissue. From a therapeutic perspective, there is always a need for minimally invasive methods to treat breast cancers, particularly to maintain cosmesis within the treated breast and minimize the risk of lymphedema associated with axillary lymph node dissection. While hyperthermia therapy is still considered experimental, and much more research is needed before it can be widely used in clinical practise, hyperthermia using gold nanoparticles may be beneficial in the future. For particular cases, such as positive sentinel lymph, noninvasive imaging with gold nanoparticles can also aid in determining whether to forego axillary lymph node partition nodes [28], which to date has not met with wide acceptance.

VII. CONCLUSIONS

Gold nanoparticles may either accumulate in tumor tissue passively through the EPR effect or actively through conjugation with a specific molecule. With an NIR laser, gold nanoparticles can induce hyperthermia through plasmon resonance. Gold's high atomic number aids in the enhancement of radiotherapy results, which can be enhanced by moderate laser-induced hyperthermia. From cellular uptake and imaging in vitro to survival improvement in vivo, researchers have studied the use of gold nanoparticles

in breast cancer. Although gold nanoparticles are less toxic than other metallic nanoparticles, problems like lack of clearance and more specific tumor cell targeting must be solved before they can be used in clinical trials. Early clinical trials of gold nanoparticles in patients with lung cancer (NCT01679470) and head and neck cancer (NCT00848042) will provide new insights into these particles' use and inform their application in breast cancer patients.

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