# Fundamentals and Applications of Pulsed Laser Gene and Drug Delivery from Lipid Nanoparticles containing Gold Nanoparticles

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Lipid-based nanoparticles (LNPs) are rationally designed 100nm spherules of concentric biodegradable phospholipids able to entrap many water or lipid-soluble therapeutic cargos. As such, LNPs hold great potential in the development of gene and drug-delivery-based applications as they further exhibit numerous attractive properties, such as long-term stability in biological environments [1]. They can be further designed to exhibit the ability to release their cargo in the presence of a trigger, either locally (pH changes or enzymes), or remotely (ultrasound, light, magnetic field) [1-2]. Here we propose a pulsed laser-triggered release approach based on the interaction of a single laser pulse with (5nm) gold nanoparticles (AuNPs) contained within engineered LNPs [3], resulting in rapid release of encapsulated therapeutic cargos. (see Figure 1) We have examined two different approaches of triggered release, by performing both simulations and experiments.

In the first approach [4], a nanosecond laser pulse is employed for the release of the anti-cancer drug Doxorubicin (DOX) from LNPs. The latter are engineered oligolamellar vesicles containing clustered AuNPs within junctions of lipid bilayers and DOX at their aqueous core [3]. The laser is tuned near the plasmon resonance of the AuNPs leading to induction of opening of the LNP. We demonstrate through simulation and experimentally that laser irradiation leads to sufficiently high temperatures for thermal decomposition of the surrounding lipids near the AuNPs, yet, without affecting the integrity of the drug [4]. Overall, the demonstrated increased efficacy of the proposed approach in the treatment of human breast adenocarcinoma cells *in vitro* holds promise for further improvements in cancer chemotherapy strategies [4].

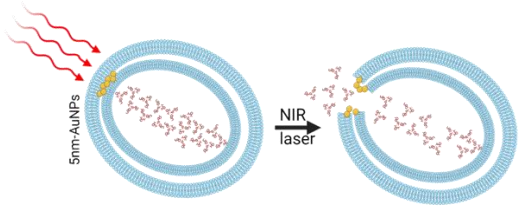


Figure 1: Schematics of laser trigger Gene/Drug release from Lipid Nanoparticles containing small gold nanoparticles

The second approach consists of laser-triggered liberation of genetic material instead of DOX. In this case, a femtosecond laser pulse is employed to interact with the clustered AuNPs out of the plasmon resonance. The LNP opening mechanism is proposed based on plasmon-induced hot spots of broadband laser-field amplification leading to highly localized photochemical decomposition of the surrounding lipid chains and release of the encapsulated substances. We, therefore, propose applying triggered gene release by ultrashort laser pulses in ophthalmology, specifically for retina degenerative diseases.

**References**: [1] T. M. Allen and P. R. Cullis, Adv. Drug Delivery Rev. (2013): 65, 36; [2] S. Bibi et al., J. Microencapsul (2012): 29, 262; [3] I. V. Zhigaltsev, et al., Langmuir (2022): 38, 7858; [4] A. Uzel, et al., Small 19.52 (2023): 2305591.