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Laser-induced stress waves facilitate targeted gene transfer

Shunichi Sato

Pressure waves caused by nanosecond laser pulses can be used to deliver macromolecules to cells and tissues.

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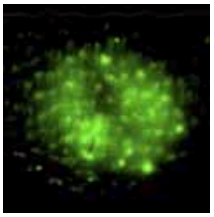

It is well established that a strong pressure wave, known as a photomechanical or laser-induced stress wave (LISW), accompanies laser-induced plasma. For medical applications, LISWs are often undesirable since they cause collateral tissue damage during laser surgery. However, an important *positive* application of LISWs is their ability to deliver drug molecules to cells and tissues. At Harvard Medical School, A. Doukas proposed the use of laser-absorbing material (the laser target), such as polymer sheets, to generate LISWs. This provides a simple method for cells or tissue to interact with LISWs but not directly with lasers. On this basis, his group has been conducting comprehensive experiments on drug delivery both in vitro and in vivo.[1]

We have extended their method to deliver macromolecules, such as genes. Gene delivery is a key technology for gene therapy and regenerative medicine, where viral vectors are widely used. However, serious side effects caused by immune response and limited targeting characteristics are discouraging the use of viral vectors for clinical application. Thus, both physical and chemical nonviral methods have recently received much attention.

Figure 1 shows a schematic of our LISW-based gene-delivery method. Plasmid DNA (circular DNA residing in bacterial cytoplasm) is used as a vector of the gene of interest. We inject the plasmid into target tissue, on which a laser target is placed, and subject the target to irradiation with a high-intensity, nanosecond laser pulse to induce plasma and hence an LISW. By placing optically transparent material on the target, the plasma is confined, resulting in an increase in the LISW's impulse. Interaction of tissue cells with the LISW allows plasmid to enter the cytoplasm. We usually use a black rubber disk covered with a polyethyleneterephthalate sheet for the laser target, which is irradiated with a 532nm, 6ns quality-switched neodymium-doped yttrium-aluminum-garnet laser pulse. Peak pressure of the LISW easily reaches several tens of megapascals, the pulse width is on the order of microseconds, and the pressure is compressive (not tensile), thus enabling minimally invasive tissue interaction.

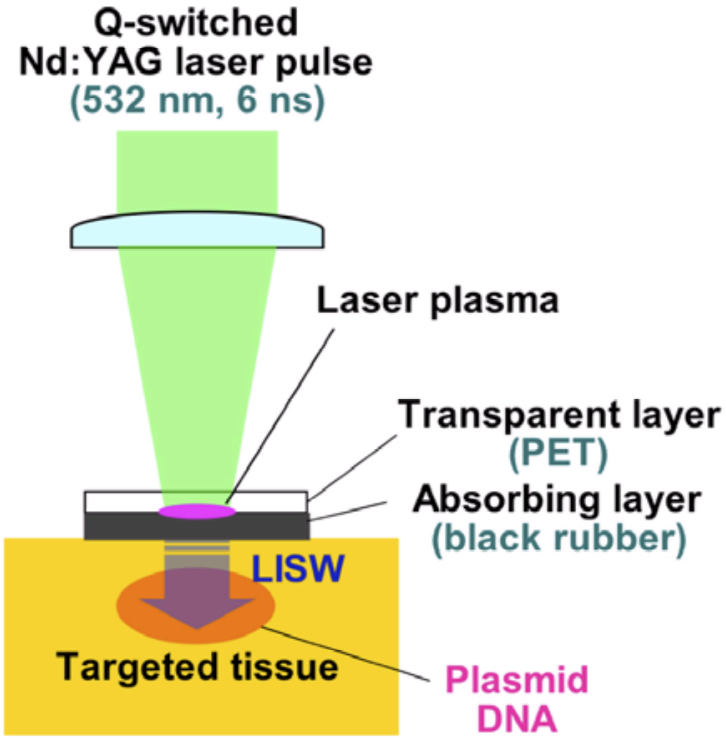

Figure 1. Schematic of our gene-transfer method using laser-induced stress waves (LISWs). PET: Polyethyleneterephthalate. Nd:YAG: Neodymium-doped yttrium aluminum garnet. Q-switched: Quality-switched.

We have demonstrated successful in vivo gene transfer to various tissues in rodents (see Figure 2). For instance, plasmid coding for enhanced-green-fluorescent protein was injected intradermally into rat skins and a laser target was irradiated with three laser pulses, characterized by a spot diameter of 3mm at a fluence of 1.9J/cm^2. We observed strong gene expression only in the area corresponding to the laser spot in the epidermis, demonstrating highly site-specific gene transfer.[2] Gene transfer to nondividing cells, such as nerve and muscle cells, is difficult using conventional methods. However, efficient gene expression was obtained in mouse brain[3] and rat tibial muscle using LISWs, although chemical agents (polyethylenimine and bupivacaine hydrochloride, respectively) were also used simultaneously. We observed gene expression at a depth of ~3.5mm in the brain and at depths of 6–7mm in the muscle, indicating that LISWs can be used to treat deep tissue. Efficient gene transfer was also achieved for the retina and spinal cord in rats (no chemical agents were used in these cases).

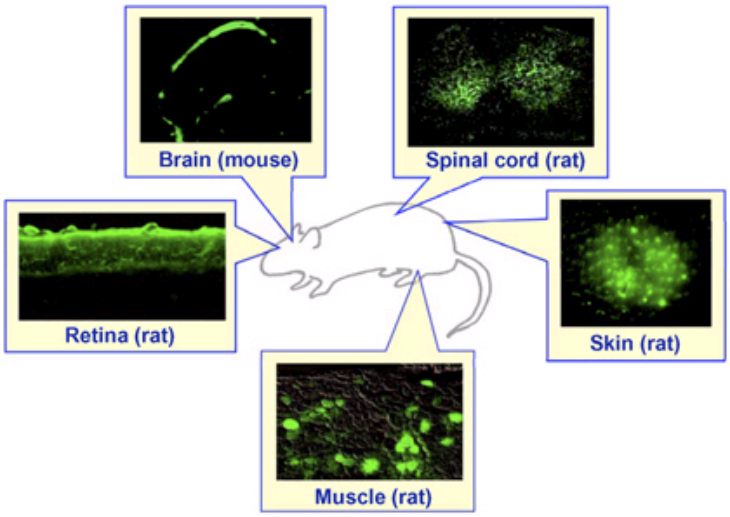

Figure 2. In vivo targeted gene transfer to various tissues in rodents using LISWs. Green fluorescence indicates expression of an enhanced-green-fluorescent protein gene.

Reporter genes without therapeutic effects were used in gene delivery, but we also demonstrated therapeutic effects based on our gene-transfer method. We transferred hepatocyte growth-factor gene to rat skin grafts using LISWs to accelerate their adhesion after grafting (see Figure 3). We performed autografting, which led to significantly enhanced reepithelialization (as well as angiogenesis[4] and reperfusion), thus demonstrating the gene-transfer

efficacy for accelerated adhesion. Early adhesion is one of the key requirements for successful transplantation.

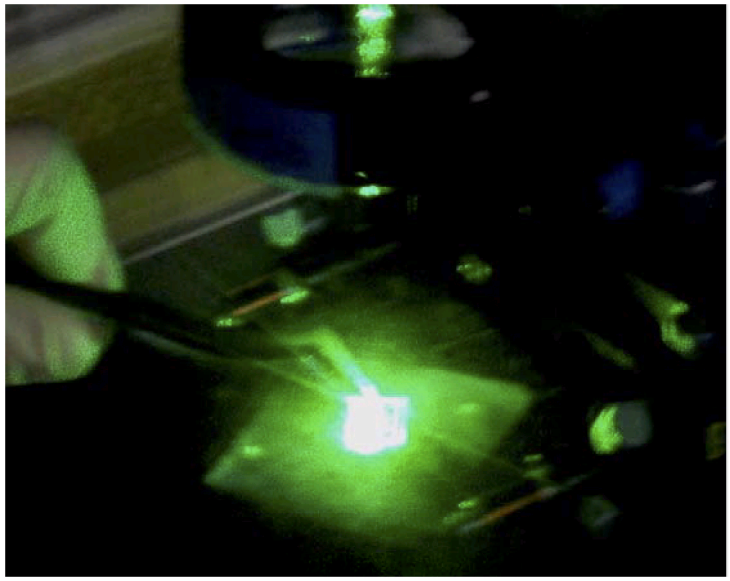

Figure 3. Transfer of hepatocyte growth-factor gene to a skin graft using LISW.

Nonviral, targeted gene delivery is a key technology that determines the outcome of gene therapy and regenerative medicine, for which LISWs will be an important tool. Our next step towards clinical application will be to further demonstrate therapeutic effects based on our gene-transfer method. Gene-therapy experiments for spinal-cord and traumatic brain injury are currently underway. Development of a catheter-based gene-transfer system is also important to extend the application area.

This work is conducted in close collaboration with Minoru Obara's group at Keio University.

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References:

1. A. G. Doukas, N. Kollias, Transdermal drug delivery with a pressure wave, *Adv. Drug Deliver. Rev*. 56, pp. 559-579, 2004.

2. M. Ogura, S. Sato, K. Nakanishi, M. Uenoyama, T. Kiyozumi, D. Saitoh, T. Ikeda, H. Ashida, M. Obara, In vivo targeted gene transfer in skins by the use of laser-induced stress wave, *Lasers Surg. Med*. 34, pp. 242-248, 2004.

3. Y. Satoh, Y. Kanda, M. Terakawa, M. Obara, K. Mizuno, Y. Watanabe, S. Endo, H. Ooigawa, H. Nawashiro, S. Sato, K. Takishima, Targeted DNA transfection into the mouse central nervous system using laser-induced stress waves, *J. Biomed. Opt*. 10, pp. 060501, 2005. doi:10.1117/1.2128432

4. M. Terakawa, S. Sato, D. Saitoh, H. Tsuda, H. Ashida, H. Okano, M. Obara, Enhanced angiogenesis in grafted skins by laser-induced stress wave-assisted gene transfer of hepatocyte growth factor, *J. Biomed. Opt*. 12, pp. 034031, 2007. doi:10.1117/1.2745313

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