***IN SITU* DRUG SYNTHESIS AT CANCER CELLS
FOR MOLECULAR TARGETED THERAPY BY
MOLECULAR LAYER DEPOSITION
-CONCEPTUAL PROPOSAL-**

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17.1. INTRODUCTION

Molecular targeted drugs have been developed as ideal substances to overcome cancer. Antibody drugs are promising for efficient and safe drug delivery. Antibodies with attached strong cancer killing drugs enable exact targeting to attack cancer cells with small side effects. Antibodies with attached quantum dots enable the imaging of cancer cell distributions [1], those with attached paramagnetic agents enable labeling for a magnetic resonance imaging system (MRI) [2], and those with attached radioactive compounds enable enhanced radiotherapy [3]. One drawback of antibody drugs is their large molecular weight. This prevents them from attacking the inside of cancer cells, limiting the efficacy of these drugs to areas outside cancer cells.

On the contrary, low molecular weight drugs can pass through cell membranes, attacking the inside of cancer cells. One drawback of these drugs is the side effects caused by imperfect targeting selectivity.

Recently, it was revealed that the destruction of cancer stem cells is essential to achieve perfect healing, and many approaches have attempted to attack cancer stem cells. The difficulty in destroying cancer stem cells is based on several factors [4] such as the excretion of drugs by adenosine triphosphate (ATP)-binding cassette (ABC) transporters, cell protection *via* cell cycle arrest, and reducing systems to protect from oxidative stress.

In the present chapter, the concepts of molecular targeted drug delivery utilizing *in situ* drug synthesis at cancer cell sites by the molecular layer deposition (MLD) [5-7] are described. MLD is a monomolecular-step synthesis process for tailored organic materials, in which molecules are connected one by one in designated sequences. This technique is expected to provide improved ways to carry drugs to cancer cells and cancer stem cells without attacking normal cells [8].

In addition, the concept of laser surgery utilizing a self-organized lightwave network (SOLNET) [9-11], which enables self-aligned optical waveguide construction toward luminescent targets, is proposed.

MLD and SOLNET are technologies that have been developed in the photonics, optoelectronics, and electronics fields. All the experimental results presented in this chapter were obtained in these fields, including photovoltaics, electro-optic devices, and optical interconnects within computers. It would be author's great pleasure if the concepts proposed here would be evaluated by researchers in the biomedical field.

17.2. MOLECULAR LAYER DEPOSITION (MLD)

MLD is a monomolecular-step synthesis process for tailored organic materials. Although MLD was developed for applications in the fields of photonics, optoelectronics, and electronics, MLD may also be applicable to molecular targeted drug delivery to cancer cells. In this section, the concept and featured capabilities of MLD are reviewed.

17.2.1. Concept

MLD is a precisely-controlled synthesis process for tailored organic materials with designated molecular arrangements [5-7]. The concept of MLD is shown in Figure 1, where four kinds of source molecules, Molecules A, B, C, and D, are used. MLD is achieved by selective chemical reactions or electrostatic forces between source molecules. They are prepared under the following guidelines, that is, the same kind of molecules cannot be combined, and different kinds of molecules can be combined. Therefore, in Figure 1, Molecules A-B, B-C, C-D, and D-A can be formed, while Molecules A-A, B-B, C-C, and D-D cannot be formed.

Figure 1. Concept of MLD

First, Molecule A is provided to a substrate in order to connect it to the connecting sites of the substrate. Once the connecting sites are covered with Molecule A, the deposition of Molecule A is automatically terminated because the same source molecules cannot be combined. This is called the self-limiting effect, which is utilized in atomic layer deposition (ALD) [12]. Next, molecules are switched from A to B to connect Molecule B to Molecule A. When Molecule A is covered with Molecule B, the deposition of Molecule B is automatically terminated. By repeating this process from B to C, from C to D, and so on, a tailored organic material with a monomolecular-step sequence of A/B/C/D/--- is synthesized.

MLD utilizing selective chemical reactions can be performed with source molecules having two or more reactive groups such as -NH_2 , -CHO , -NCO , -OH , -COOH , acid anhydride groups, and epoxy groups. MLD utilizing the electrostatic forces can be performed with molecules possessing an electric charge. MLD can be carried out either in the vapor phase or in the liquid phase.

Figure 2 shows an experimental proof-of-concept of MLD using pyromellitic dianhydride (PMDA) and 4,4'-diaminodiphenyl ether (DDE) [5]. When *p*-phenylenediamine (PPDA) is provided onto a DDE surface, the film thickness, which was monitored by a quartz crystal microbalance, rapidly increases and is then saturated. When the molecules are switched from PPDA to DDE, again, the film thickness rapidly increases and is saturated. By repeating molecule switching, step-like film growth is observed. The thickness change for one growth step is close to the sizes of PMDA and DDE. These results indicate that monomolecular-step synthesis is performed by MLD.

Figure 2. Experimental demonstration of MLD utilizing two kinds of source molecule, PMDA and DDE

17.2.2. Capabilities

Three featured capabilities of MLD are schematically depicted in Figure 3. Due to the self-limiting effect, MLD enables “ultra-thin/conformal organic material synthesis” on arbitrary structures, including porous, deforming, and floating objects. MLD enables “tailored organic material synthesis” with artificially-controlled molecular sequences as explained above in Figure 1. MLD also

enables “selective organic material synthesis.” Due to these capabilities, MLD has provided a variety of applications in the fields of photonics, optoelectronics, and electronics. Bent *et al.* succeeded in forming copper diffusion barriers in large-scale integrated circuits [13] and depositing photoresists [14] by MLD. Weimer and Liang achieved a uniform polymer film coating on surfaces of nano-particles [15]. The George group developed a growth process of hybrid organic-inorganic polymer films by combining MLD with ALD [16]; the films were used as gate insulators for organic thin-film transistors [17] and thin-film encapsulations for organic light-emitting diodes [18]. MLD has also been applied to photovoltaic devices [6,7,19-21] and electro-optic devices [6,7,22,23].

The ability of MLD to synthesize tailored organic materials at selected sites is especially important in the application to molecular targeted drug delivery to cancer cells. In Sections 17.3 and 17.4, details of the tailored organic material synthesis and the selective organic material synthesis, namely, *in situ* organic material synthesis at selected sites, are reviewed.

Figure 3. Three featured capabilities of MLD

17.3. TAILORED ORGANIC MATERIAL SYNTHESIS

One of the examples of tailored organic material synthesis by MLD is the fabrication of polymer multiple quantum dots (MQDs) [20,21,24] using three source molecules, *i.e.* terephthalaldehyde (TPA), *p*-phenylenediamine (PPDA) and oxalic dihydrazide (ODH). TPA has two -CHO groups, while PPDA and ODH have two -NH_2 groups. TPA and PPDA are connected with a double bond generated by a reaction between -CHO and -NH_2 , allowing π -electron delocalization over the entire produced molecule. TPA and ODH produce a molecule containing a series of single bonds, which severs the π -electron wavefunction. Quantum dots (QDs) can be formed in polymer wires using these bond characteristics.

Figure 4 shows an example of the MLD process in which source molecules are connected in the sequence -ODH-TPA-PPDA-TPA-ODH---, to construct a polymer QD with an OTPT structure.

Figure 4. MLD process to construct a polymer QD with an OTPT structure

Figure 5. 3QD polymer MQD containing QDs with OT, OTPT and OTPTPT structures

Figure 5 shows a polymer MQD named “3QD” containing three kinds of QDs: OT, OTPT, and OTPTPT. The 3QD polymer MQD is synthesized with a molecule switching sequence of -ODH-TPA-ODH-TPA-PPDA-TPA-ODH-TPA-PPDA-TPA-PPDA-TPA-ODH---. The regions involving ODH are barriers. The region between the two ODHs is regarded as a QD, where the π -electron wavefunction is delocalized. In the region of OTPTPT, molecules are connected in the sequence -ODH-TPA-PPDA-TPA-PPDA-TPA-ODH-, and the QD length is ~ 3 nm. For OTPT, the QD length is ~ 2 nm, and for OT ~ 0.8 nm.

Figure 6 shows the absorption peak shifts to shorter wavelengths (higher energies) in the trend OTPTPT, OTPT, then OT. This trend follows that of decreasing QD length, and is attributed to the changing degree of quantum confinement of π -electrons in the QDs.

Figure 6. Absorption spectra of OT, OTPT, OTPTPT, and 3QD polymer MQD

Figure 7. Absorption peak energy of OT, OTPT, and OTPTPT plotted as a function of QD length

In Figure 7, experimental results of the absorption peak energy of OT, OTPT and OTPTPT structures are shown as a function of QD length. Results derived from the quantum confined model for QDs are also presented. The experimental and calculated values are in good agreement, suggesting that the absorption peak shift is attributed to the electron confinement by the QDs.

As can be seen in Figure 6, the 3QD polymer MQD exhibits a broad absorption band extending from ~ 300 to ~ 480 nm, which is attributed to the superposition of component absorption bands of OT, OTPT and OTPTPT structures.

Thus, we have successfully controlled the molecular arrangement in polymer wires with designated sequences of three molecules using MLD, and fabricated polymer MQDs, suggesting the possibility of synthesizing drugs in monomolecular steps by MLD.

17.4. IN SITU ORGANIC MATERIAL SYNTHESIS AT SELECTED SITES

We have developed several techniques to synthesize organic materials at selected sites. In this section, selective growth processes utilizing hydrophilic/hydrophobic surface characteristics and anchoring molecules are described.

17.4.1. Hydrophilic/hydrophobic surfaces

Figure 8 shows examples of selective growth utilizing hydrophilic/hydrophobic surface characteristics [7]. When TPA and PPDA molecules are provided onto a glass substrate with a patterned triphenyldiamine (TPD) coating, poly-azomethine (poly-AM) is selectively grown on the hydrophilic glass surface as shown in Figure 8(a). No poly-AM is grown on the hydrophobic TPD surface.

Figure 8. Selective growth utilizing hydrophilic/hydrophobic surface characteristics

The same selective growth of poly-AM can be observed by using hexamethyl-disilazane (HMDS) instead of TPD [25]. Such selectivity occurs due to the fact that the PPDA and TPA molecules weakly adsorb on hydrophobic surfaces while they strongly adsorb on hydrophilic surfaces.

Figure 8(b) shows selective growth of polymer MQDs of the OT structure grown by MLD. It was found that the polymer MQD film grows only on TiO_2 . On ZnO, no film grows. This might be because ZnO exhibits weak hydrophilic characteristics.

17.4.2. Anchoring molecules with chemical reactions

Figure 9 shows a process for selective growth utilizing anchoring molecules with chemical reactions [26]. First, molecules such as amino-alkanethiol are distributed. The molecules are selectively adsorbed on sites with Au atoms. Next, TPA molecules are provided, then they connect to amino-alkanethiol molecules by chemical reactions between $-\text{CHO}$ and $-\text{NH}_2$. Next, PPDA molecules are provided to connect them to TPA molecules. By repeating these steps, poly-AM is selectively grown at Au sites. In this process, the amino-alkanethiol molecules act as anchoring molecules to initiate material synthesis at the sites.

Figure 9. Process of selective growth by MLD utilizing anchoring molecules with chemical reactions to synthesize organic materials on Au

Figure 10. FTIR-RAS spectra for poly-AM grown on Au by MLD

In order to examine the anchoring effect of amino-alkanethiol molecules on selective growth, poly-AM was grown on glass substrates with Au films by MLD in the following two procedures. The first is denoted by “with amino-alkanethiol,” in which poly-AM grew after distributing amino-alkanethiol over the Au film surface in a solvent. The second is denoted by “without amino-alkanethiol,” in which poly-AM grew on the Au film surface without amino-alkanethiol. Figure 10 shows the Fourier transform infrared reflection absorption spectroscopy (FTIR-RAS) spectra of the Au film surface after providing TPA to it to perform Step 1 in Figure 9. The absorption peaks attributed to TPA in wavenumber regions around 820 cm^{-1} and 780 cm^{-1} are larger with amino-alkanethiol than without amino-alkanethiol. When the substrate temperature was raised to $45\text{ }^{\circ}\text{C}$, the peak height without amino-alkanethiol decreased while that with amino-alkanethiol did not decrease. These results indicate that, in the case with amino-alkanethiol, more TPA molecules existed on the Au film surface with stronger adsorption strengths *via* the amino-alkanethiol anchoring molecules compared to the case without amino-alkanethiol.

From the TPA connected to the amino-alkanethiol molecule, poly-AM was grown in Step 6, confirming the anchoring effect of the amino-alkanethiol molecules toward Au sites [26]. Such an anchoring effect that initiates material synthesis in MLD might be applied to the *in situ* drug synthesis at cancer cell sites, as discussed in Section 17.5.

Figure 11. Concept of seed-core-assisted MLD for three-dimensional synthesis

In addition, the concept of seed core-assisted MLD is briefly described. As Figure 11 shows, by depositing anchoring molecules of amino-alkanethiol on patterned Au objects, self-assembled monolayers (SAMs) are formed on the top and side walls of them. We call the objects with SAMs “seed cores.” Vertical growth of polymer wires are initiated by the SAM on the top of the seed core while horizontal growth occurs *via* the SAM on the sidewall. The regions, where polymer wires should not grow are covered with, for example, an SiO₂ film. Thus, the seed cores can be used to control polymer wire growth locations and orientations. By distributing the seed cores with designated patterns, polymer wires are expected to grow with designated configurations, constructing three-dimensional polymer wire networks.

17.4.3. Anchoring molecules with electrostatic force

Selective growth utilizing anchoring molecules with electrostatic forces can be performed by liquid-phase MLD (LP-MLD) [7,19,27], in which source molecules in the solvent are provided to objects in the liquid phase.

The proof-of-concept was demonstrated by using source molecules illustrated in Figure 12. The terms “p-type” and “n-type” were defined by Meier [28]. Rose Bengal (RB), eosin (EO) and fluorescein (FL) are p-type molecules, which tend to have a negative charge by accepting electrons. Crystal violet (CV) and brilliant green (BG) are n-type molecules, which tend to have a positive charge by donating electrons.

An LP-MLD process to synthesize organic materials on ZnO, which is an n-type semiconductor, is shown in Figure 13. The synthesis is performed with a molecule switching sequence of p-type molecule (p1) → n-type molecule (n1) → p-type molecule (p2) to construct a p1/n1/p2 structure. Here, due to the attractive force induced by the positive charge of ionized donors in the n-type ZnO and the negative charge in the p-type molecules, the p-type molecules are strongly connected on ZnO. Similarly, due to the attractive force induced by the positive charge in the n-type molecules and the negative charge in the p-type

molecules, the n-type molecules and the p-type molecules are strongly connected to each other. The same type of molecule does not connect due to the repulsive force between them. This interaction scheme between p-type molecules and n-type molecules satisfies the condition for MLD depicted in Figure 1.

Figure 12. Source molecules for selective growth utilizing anchoring molecules with electrostatic forces by LP-MLD

Figure 13. Process of selective growth by LP-MLD utilizing anchoring molecules with electrostatic forces to synthesize organic materials on ZnO

In the LP-MLD process shown in Figure 13, molecule p1 can be regarded as an anchoring molecule toward ZnO to initiate the synthesis of the p1/n1/p2 structure at the ZnO site.

Figure 14 shows photographs of the LP-MLD cell during the synthesis of a two-molecule stacked structure of ZnO/RB/CV. A ZnO substrate was placed in the cell, and solutions of source molecules of RB and CV were sequentially injected into the cell. The substrate was exposed to each solution of source molecules for ~ 5 min. The molecule concentration of the solution was 1.6 mol L^{-1} . Rinse processes were used prior to source molecule switching. Namely, LP-MLD was carried out with sequential steps of RB injection, rinse, CV injection, and rinse.

Figure 14. LP-MLD to synthesize a two-molecule stacked structure of ZnO/RB/CV

To analyze the stacked structures of molecules synthesized on ZnO by LP-MLD, the surface potential was measured. Source molecules were introduced to ZnO powder layers formed on glass substrates with indium tin oxide (ITO) electrodes.

The surface potential of the plain ZnO layer before LP-MLD was found to be about -200 mV , which is attributed to negative electric dipole moments generated on the ZnO surface by electrons donated from zinc atoms in interstitial sites to oxygen adsorbed on the surface. When p-type molecules are adsorbed onto the ZnO layer, as shown in Figure 15, the surface potential becomes more negative. This is attributed to the additional negative electric dipole moments generated by the negative charge in the p-type molecules on the ZnO surface [29]. Conversely, when n-type molecules are adsorbed onto

the ZnO layer, the surface potential becomes less negative. This is attributed to the positive charge in the n-type molecules on the ZnO surface [29].

For the two-molecule stacked structure of ZnO/RB/CV, the surface potential becomes less negative compared to the surface potential of the plain ZnO. This is caused by the positive charge in the n-type molecules on the top of the stacked structure [29]. For the three-molecule stacked structure of ZnO/RB/CV/EO, the surface potential becomes more negative compared to the surface potential of the plain ZnO. This is caused by the negative charge in the p-type molecules on the top.

From these results, it is suggested that multi-molecule stacked structures are definitely synthesized on ZnO by LP-MLD using p-type and n-type molecules.

Figure 15. Surface potential of ZnO with single- and multi-molecule stacked structures synthesized by LP-MLD

Using RB for p-type molecules and CV for n-type molecules, we demonstrated the anchoring effect. As shown in Figure 16, when CV is provided on a ZnO layer in the solvent, the ZnO surface remains white, indicating that little CV is adsorbed on ZnO. This means that immobilization of CV on ZnO sites is not possible.

When RB is provided on a ZnO layer in the solvent, the ZnO surface becomes pink, indicating that RB is adsorbed on ZnO. When CV is provided on the

RB-adsorbed ZnO layer in solvent, the ZnO surface becomes blue, which is the color of CV, indicating that much CV is adsorbed on ZnO *via* RB. These results indicate that immobilization of CV on ZnO sites is achieved by RB. This implies that RB acts as the anchoring molecule to immobilize CV on ZnO sites.

The anchoring mechanism demonstrated in Figure 16 is expected to be applied to the molecular targeted drug delivery utilizing *in situ* drug synthesis at cancer cell sites by MLD, as discussed in Section 17.5.

Figure 16. Immobilization of CV on ZnO sites by anchoring molecules of RB

17.5. MOLECULAR TARGETED DRUG DELIVERY BY *IN SITU* SYNTHESIS AT CANCER CELLS

As mentioned in Section 17.2.4., MLD has the potential to be applied to molecular targeted drug delivery. The anchoring mechanisms shown in Figures 9 and 13 can be used to initiate *in situ* drug synthesis at particular sites. LP-MLD is analogous with *in situ* drug synthesis within a human body [7,8,19,30] because the human body is a liquid system. The human body is regarded as the MLD cell and cancer cells are the substrate. In the present section, three examples of selective drug delivery with *in situ* drug synthesis at

cancer cells by LP-MLD are proposed for low molecular weight drugs and antibody drugs.

17.5.1. Low molecular weight drugs into cancer cells

Low molecular weight drugs have the advantage that they can pass through cell membranes and attack the inside of cancer cells. However, as illustrated in Figure 17, they have a drawback in that they attack normal cells while attacking cancer cells due to their imperfect targeting selectivity, resulting in side effects.

For example, gefitinib shuts down intracellular signal transduction in cancer cells by binding to the epidermal growth factor receptor (EGFR). This is an effective molecular targeted drug for lung cancer; however, it causes interstitial pneumonia as a side effect.

Figure 17. Side effects caused by low molecular weight drugs

If *in situ* synthesis of a toxic drug can be done selectively within cancer cells by connecting small non-toxic component molecules using LP-MLD, selective delivery of the toxic drug into targeted cancer cells might be achieved without attacking normal cells, namely, without side effects.

Figure 18 shows a conceptual illustration of an LP-MLD process for molecular targeted drug delivery. The toxic drug is divided into several non-toxic component molecules. In this example, the toxic drug is decomposed into five

component molecules; Molecules A, B, C, D, and E, which have reactive groups for performing the LP-MLD process.

Figure 18. Conceptual illustration of an LP-MLD process for *in situ* synthesis inside cancer cells for low molecular weight drug delivery

First, Molecule A is injected into a human body. Molecule A is selectively connected to the ATP-binding sites of the tyrosine kinase domain of EGFR. Here, Molecule A acts as the anchor at the ATP-binding site. After excess

Molecule A is excreted from the human body, Molecule B is injected to be selectively connected to Molecule A. By successive injections of Molecules C, D, and E, the synthesis of the toxic drug is completed. The synthesized drug acts as a tyrosine kinase inhibitor, which disconnects intracellular signal transduction in cancer cells by protecting ATP from binding to ATP-binding sites, thus suppressing cancer growth.

17.5.2. Antibody drugs to cancer cells

Figure 19 shows an LP-MLD process to stack different kinds of functional molecules on cancer cells one by one with designated arrangements. First, Molecule A, which is an antibody, is injected into the human body to be selectively attached to cancer cells as an anchor for the initiation of synthesis, then excess molecule A is excreted from the body. Next, Molecule B, which is a luminescent agent for imaging, is injected to be connected to Molecule A. Similarly, by successively injecting Molecule C, which is a sensitizer for photo-dynamic therapy (PDT), and D, which is a radio-enhancement agent, multi-functional materials having the structure A/B/C/D can be constructed on cancer cells.

Figure 19. Conceptual illustration of an LP-MLD process for *in situ* synthesis on cancer cells in antibody drug delivery

17.5.3. Drugs into cancer stem cells

It is known that the destruction of cancer stem cells is important to achieve perfect healing of cancer. The difficulty in the destruction of the cancer stem cells is due to several factors such as the excretion of drugs by ABC transporters, cell protection by cell cycle arrest, and reducing systems to protect from oxidative stress. In the present subsection, a proposal for the suppression of drug excretion by ABC transporters is proposed.

Figure 20. Model of drug excretion by ABC transporters

Figure 20 shows a model for drug excretion by ABC transporters. Rapamycin, which is an inhibitor of the mammalian target of rapamycin (mTOR), is known as a molecular targeted drug against leukemic stem cells. The drug is carried away from cancer stem cell sites by ABC transporters distributed in the surrounding region. This reduces the ability of the drug to attack cancer stem cells.

One possible way to solve this problem may be drug delivery by LP-MLD, as conceptually illustrated in Figure 21. The drug is divided into several component molecules, say, five component molecules of Molecules A, B, C, D, and E, that can easily pass by ABC transporters and reach cancer stem cells. First, Molecule A is injected into the human body to be selectively connected to mTOR within cancer stem cells. Molecule A acts as an anchor for mTOR. After excess Molecule A is excreted from the body, Molecule B is injected to be connected to Molecule A. By successive injections of Molecules C, D, and E, the drug is synthesized. It acts as an mTOR inhibitor, which disconnects intracellular signal transduction in cancer stem cells, enabling cancer growth suppression.

Figure 21. Conceptual illustration of the LP-MLD process for *in situ* synthesis inside cancer stem cells in molecular targeted drug delivery

17.6. LASER SURGERY BY A SELF-ORGANIZED LIGHTWAVE NETWORK (SOLNET)

A reflective self-organized lightwave network (R-SOLNET), which enables optical waveguides to be automatically formed toward luminescent targets [31-33], has been developed for self-aligned optical coupling in optical interconnects within computers. In this section, the possibility of R-SOLNET application to laser surgery is proposed.

17.6.1. Concept and demonstrations of SOLNET

SOLNET utilizes attractive force induced between light beams in photo-induced refractive-index increase (PRI) materials such as photopolymers, whose refractive index increases upon light beam exposure. Figure 22 shows a concept of R-SOLNET utilizing luminescent targets [31-33]. An optical device such as an optical fiber and luminescent targets are put in a PRI material. A write beam is introduced from the optical device into the PRI material. A part of the write beam is absorbed by the luminescent targets followed by luminescence from them. The luminescence induces the “pulling water” effect to grow R-SOLNET between the optical device and the luminescent targets. Namely, because the refractive index increases more rapidly in the region where the write beam and the luminescence overlap than in the surrounding region, the write beam and luminescence attract each other to merge by self-focusing. This enables us to construct self-aligned coupling waveguides between the optical device and the luminescent targets automatically.

Figure 22. Concept of R-SOLNET utilizing luminescent targets

We have performed experimental demonstrations of R-SOLNET formation between a multimode (MM) optical fiber with core diameter of 50 μm and a luminescent target of tris(8-hydroxyquinolino)aluminum (Alq3) powder dispersed in polyvinyl alcohol (PVA). As shown in Figure 23, a luminescent target put on an optical fiber edge is placed in a PRI material, which is a mixture of Norland Optical Adhesive NOA65 ($n = 1.52$), NOA81 ($n = 1.56$), and a sensitizer of crystal violet (CV), together with an MM optical fiber.

Figure 23. Experiment of R-SOLNET formation between an MM optical fiber and a luminescent target of Alq3-dispersed PVA

When a write beam with a wavelength of 405 nm is emitted from the MM optical fiber, green/blue luminescence is generated from the luminescent target. At the same time, red luminescence from CV doped in the PRI material is observed, which enables us to trace R-SOLNET formation. With writing time, SOLNET is formed toward the luminescent target, and finally the optical fiber and the target are connected by R-SOLNET, providing a proof-of-concept of R-SOLNET utilizing luminescent targets. This indicates that the R-SOLNET can be constructed toward a micrometer-order scale target. Figure 24 shows an experimental demonstration of R-SOLNET toward two luminescent targets. It is found that a branching R-SOLNET connects an MM optical fiber on the left to two luminescent targets on the right.

These results suggest the possibility of SOLNET-assisted laser surgery. The method is expected to be applied for the selective removal of scattered small cancer cells, to which luminescent molecules are adsorbed before laser exposure.

Figure 24. Experimental demonstration of R-SOLNET formation toward two targets

17.6.2. SOLNET-assisted laser surgery

Figure 25 shows the concept of the SOLNET-assisted laser surgery [7,8]. First, luminescent molecules are adsorbed onto cancer cells by LP-MLD. After inserting an optical fiber and a PRI material into the region surrounding the cancer cells, a write beam is introduced from the optical fiber to form R-SOLNET that connects the optical fiber to the cancer cells. By introducing surgery laser beams into the R-SOLNET *via* the optical fiber, cancer cells are

destroyed selectively. By detecting the backward luminescence emitted from the luminescent molecules, *in situ* monitoring of the degree of cancer cell destruction might be possible.

For practical applications of SOLNET to laser surgery, it is necessary to select appropriate non-toxic PRI materials.

Figure 25. Concept of SOLNET-assisted laser surgery

Figure 26 shows the concept of SOLNET-assisted photodynamic therapy (PDT), in which two-photon photochemistry is used [7,30]. In molecules with two-photon photochemistry, an electron is excited by a photon with a wavelength of λ_1 from the S_0 state to the S_n state, when then transfers to the T_1 state, and is finally excited to the T_n state by a photon with another wavelength of λ_2 to induce chemical reactions for attacking cancer cells. This mechanism enables us to widen the region where PDT is effective, as mentioned below.

In conventional PDT, the excitation light cannot reach the deepest regions containing cancer cells. By using two-photon photochemistry, three-dimensional attack on cancer cells might be possible because the chemical reactions occur only in regions where photons with λ_1 and photons with λ_2 coexist. Therefore, the chemical reactions can be selectively induced in any

region we want by controlling the position of the light beams of the two different wavelengths.

As illustrated in Figure 26, first, luminescent molecules with the two-photon photochemistry are adsorbed into cancer cells. After forming the R-SOLNET that stretches toward the cancer cells, surgery beams of λ_1 are emitted from the R-SOLNET toward the cancer cells. At the same time, surgery beams of λ_2 are introduced so that the λ_1 beams and the λ_2 beams overlap in the area containing cancer cells. Thus, cancer cells located in deeper parts are destroyed.

Although many molecules with two-photon photochemistry are known, such as porphyrin, biacetyl, comphorquinone, benzyl, *etc.* [34], in order to apply them to the human body, more advanced molecules that can be safely dissolved in blood and exhibit light absorption with λ_1 and λ_2 in a range of 600–1000 nm, where light absorption due to hemoglobin is weak, should be researched.

Figure 26. Concept of SOLNET-assisted PDT utilizing two-photon photochemistry

17.7. SUMMARY

MLD enables the *in situ* synthesis of tailored organic materials at selected sites utilizing the self-limiting effect and anchoring molecules to initiate synthesis at selected sites. This function of MLD is expected to be applied to molecular targeted drug delivery.

Because the human body is a liquid system, it is regarded as the MLD cell and cancer cells as the selected sites. By dividing a toxic drug into several non-toxic component molecules and injecting them into the body sequentially, the toxic drug is synthesized at sites where the drug should be delivered. This synthesis process may reduce side effects. The synthesized drug may be a tyrosine kinase inhibitor, an antibody with functional molecules, or an mTOR inhibitor with the goal of disrupting intracellular signal transduction in cancer stem cells to suppress cancer growth.

In addition, SOLNET-assisted laser surgery, which might be applicable to the selective removal of scattered small cancer cells, was proposed.

MLD and SOLNET have been developed in the photonics, optoelectronics, and electronics fields. The author expects that the proposed concepts will be evaluated by researchers in the biomedical field.

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