Chapter 7
Photo-Cross-Linking Reaction in Nucleic Acids: Chemistry and Applications

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Abstract DNA/RNA photo-cross-linking reactions have great potential for regulating the functions, structures, and characters of nucleic acids. The photo-responsive manner of the reactions are expected to enable spatiotemporal control of the behavior of nucleic acids, and the thermal irreversibility of the photo-cross-linked product is expected to enable construction of thermally stable nanostructured DNA.

Therefore, various artificial nucleic acids that can photo-cross-link to complementary DNA or RNA have been developed. This chapter focuses on the chemistry of these artificial nucleic acids and their application for molecular, cellular, and chemical biology, and also DNA nanotechnology, which is an interesting field for the construction of nanomaterials in a bottom-up manner, such as DNA origami.

7.1 Introduction

The photoreaction in DNA is one of the most important phenomena in the basic study of photodamage in genomic DNA. Since the first report about photo-induced pyrimidine dimer formation in double-stranded DNA by Setlow [1], many researchers have made huge efforts to understand the mechanism of the phenomenon [2–6] and the mechanism of DNA damage repair [7–11]. In this phenomenon, the cyclobutane ring formation through [2 + 2] photocycloaddition between C5 and C6 carbons on adjacent pyrimidine bases in a DNA strand is induced by UVB irradiation, and the photoproduct causes genomic damage and cell death.

Psoralen derivatives, which can photo-cross-link with C5–C6 carbons on a pyrimidine base in a DNA strand in the same manner of pyrimidine dimer formation by UVA irradiation; contrary to the case of pyrimidine dimer formation caused by UVB irradiation [12], are key compounds in the history of the development of photo-functionalized nucleic acids. Based on the findings of psoralen derivatives,

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until now, various artificial nucleic acids that can photo-cross-link with DNA or RNA with a sequence specific manner have been developed.

In this chapter, the mechanism of the photo-cross-linking reaction in nucleic acids including psoralen and other artificial DNA photo-cross-linkers is described. The application of the photo-cross-linking reaction on gene regulation, genome analysis, and DNA-based nanotechnology is also described.

7.2 Psoralen: A Natural DNA Photo-Cross-Linker

Naturally occurring plant furocoumarins, e.g., psoralen, methoxsalen, and trioxsalen (Fig. 7.1a), that can photoreact with a DNA double strand, have been used for the treatment of various skin disorders such as Atopic dermatitis, vitiligo, eczema, and cutaneous T-cell lymphoma. Psoralen derivatives effectively intercalate to the AT region of genomic DNA, and the fran ring and pyrone ring of psoralen derivative form cyclobutane ring with C5–C6 carbon on the thymine bases possessed at different two DNA strands with UVA irradiation (Fig. 7.1b). Thus, the two DNA strands can be bound covalently via a photo-cross-linked product consisting of a psoralen derivative and two thymine bases [12]. This induces cytotoxicity only at the photoirradiated area. Since the psoralen derivatives can be activated with UVA irradiation, treatment of skin disorders can be performed without significant photodamage of genomic DNA caused by UVB-induced pyrimidine dimer formation.

The photoreaction including psoralen derivative also occurs in AU regions in double-stranded RNA. Using this reaction, the secondary structures of RNAs were successfully explored [13–16].
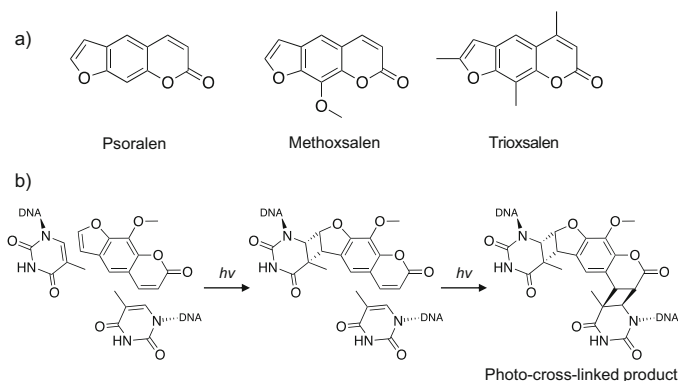

Fig. 7.1 Structure of naturally occurring plant furocoumarins (**a**) and the interstrand photo-cross-linking reaction of methoxsalen in double-stranded DNA (**b**)

7.3 Psoralen-Modified Artificial Nucleic Acids

With the development of the methodology for organic synthesis and modification of nucleic acids, psoralen derivatives have been conjugated with various synthetic oligonucleotides to give sequence specificity for the photo-cross-linking reaction of psoralen derivatives. Miller and co-workers conducted one of the most pioneering studies in this field. They introduced trioxsalen at the 5′ end of synthetic oligodeoxyribonucleotide (ODN(s)) (Fig. 7.2, Compound 1) and clearly demonstrated that the trioxsalen-modified ODN photo-cross-linked to complementary single-stranded DNA [17–19] and double-stranded DNA [20] with UVA (365 nm) irradiation. Furthermore, they also demonstrated that the trioxsalen-modified ODN having an antisense sequence for rabbit globin mRNA effectively inhibits the translation of rabbit globin mRNA in a photo-responsive manner [21]. Their findings opened the door for the development of photo-functionalized synthetic oligonucleotides. Indeed, in the early 1990s, various groups reported antisense ODN [22, 23] and triplex-forming ODN (TFO) modified with psolaren derivative [24–30]. In particular, oligonucleotide having 2′-trioxsalen-modified adenosine (Fig. 7.2, Compound 2) has the highest photoreactivity toward thymine or uracil base in a complementary DNA or RNA strand [31, 32]. Recently, coumarin-modified nucleic acid having photo-cross-linking ability to complementary DNA was reported (Fig.7.2, Compound 4 [33]). They successfully modified thymidine with coumarin using a Cu(I)-catalyzed click reaction. This is the first example of interstrand photo-cross-linking reaction by a modified pyrimidine nucleoside.
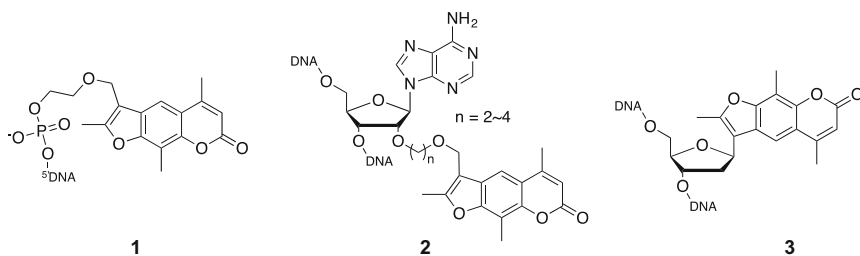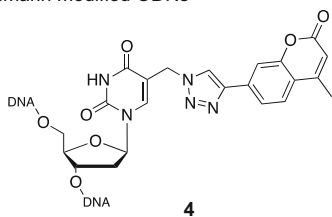

Fig. 7.2 Trioxsalen- or coumarin-modified artificial nucleic acids for DNA/RNA interstrand photo-cross-linking

7.4 3-Cyanovinylcarbazole-Modified Artificial Nucleic Acids

Owing to its photoreactivity and the ease with which it is obtained from natural plants, psoralen derivative is widely used for photo-functionalization of synthetic ODNs; however, the UVA irradiation required for the photoreaction itself sometimes causes unexpected cytotoxicity to cells. Therefore, a more highly reactive photo-cross-linker that can photo-cross-link to nucleic acids with shorter irradiation time than psoralen derivatives was required. In 2008, as a DNA photo-cross-linker having higher photoreactivity compared to psoralen derivatives, 3-cyanovinyl-carbazole-modified nucleoside (^{CNV}K) was reported by Fujimoto and co-workers ([34, 35]; Fig. 7.3, Compound 1). Similar to the case of psoralen derivatives, the photo-cross-linking reaction of ^{CNV}K occurs through a [2 + 2] photocycloaddition reaction between the vinyl moiety of ^{CNV}K and C5–C6 double bond of the pyrimidine base with 365 nm irradiation. As the photoreactivity of ODN having ^{CNV}K is at least tenfold greater than that of psoralen-modified ODNs, ^{CNV}K is the most reactive DNA photo-cross-linker at that time. Since ODN having ^{CNV}K photo-cross-link with complementary DNA or RNA [36–38], and also double-stranded DNA [39], the same as the case of psoralen derivatives, they are expected to be a powerful tool for regulating the functions of nucleic acids, the same as psoralen-modified ODNs. Most recently, a novel DNA photo-cross-linker consisting of 3-cyanovinylcarbazole and D-threoninol (^{CNV}D) has been reported ([40]; Fig. 7.3, Compound 2). As the photoreactivity of ^{CNV}D is 1.8–8-fold higher than that of ^{CNV}K, this is the most highly reactive DNA photo-cross-linker reported. Furthermore, recent research by Fujimoto's group of JAIST revealed that the complementary base of the pyrimidine base that will be cross-linked with ^{CNV}K greatly affects the photoreactivity of ^{CNV}K in double-stranded DNA [41]. Particularly, in the case of cytosine as the target of ^{CNV}K, the decrease of the hydrogen bonds between the cytosine and its complementary base by the substitution of canonical guanine with a noncanonical complementary base, such as inosine and 2-aminopurine, drastically accelerates the photoreactivity 3.6–7.7-fold. These findings suggest that the local stability and/or flexibility of the photo-cross-linking site is an important factor for
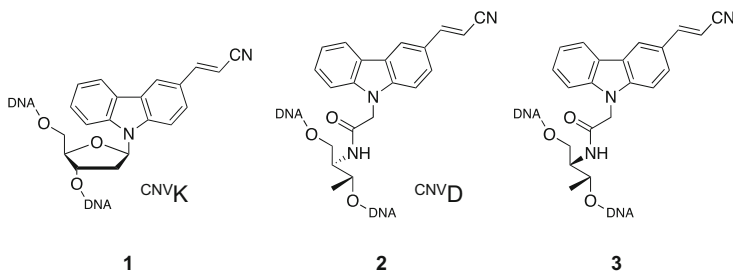

Fig. 7.3 3-Cyanovinylcarbazole-modified artificial nucleic acids for DNA/RNA interstrand photo-cross-linking

governing the photoreaction. In general, the reaction rate of the photo-cross-linking toward the cytosine base through [2 + 2] photocycloaddition is lower than that toward thymine or uracil [12, 34]. There is huge potential for improving photoreactivity toward cytosine by regulating the local stability and/or flexibility of the photo-cross-linking site with the substitution of a complementary base of cytosine.

7.5 Other Artificial Nucleic Acids

He and co-workers reported another class of DNA photo-cross-linker having a different mechanism from that of psoralen and 3-cyanovinylcarbazole derivatives: diazirine-modified nucleic acid analogue ([42]; Fig. 7.4, Compound 1). The diazirine group forms a carbene intermediate upon UVA-induced N2 elimination and cross-links to multiple nearby bases in the complementary strand. Contrary to the case of photo-cross-linking via [2 + 2] photocycloaddition, this type of photo-cross-linker can react with four kinds of nucleobases in the complementary DNA and RNA strand ([43]; Fig. 7.4, Compound 2 and 3).

As another class of the DNA photo-cross-linking reaction, recently, Asanuma's group of Nagoya University reported stilbene-modified artificial nucleic acids (Fig. 7.5 [44]). They successfully demonstrated that two complementary synthetic ODNs having stilbene moiety can photo-cross-link each other with the 340 nm irradiation through [2 + 2] photodimerization of two stilbene moieties in the double-
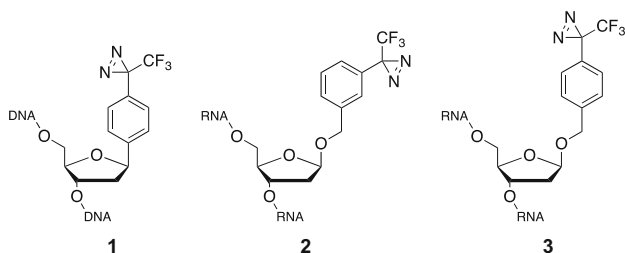

Fig. 7.4 Diazirine-modified artificial nucleic acids for DNA/RNA interstrand photo-cross-linking
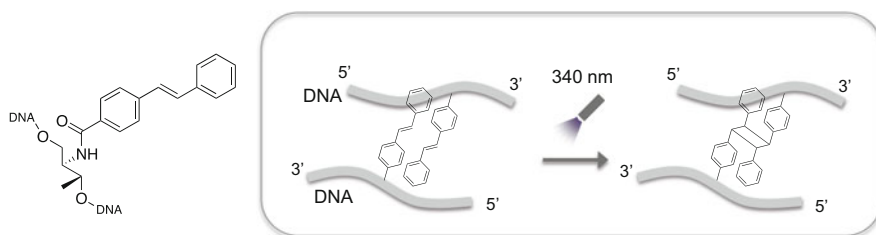

Fig. 7.5 Stilbene-modified artificial nucleic acids for DNA interstrand photo-cross-linking

stranded DNA. Contrary to the case of psoralen or 3-cyanovinylcarbazole-modified nucleic acids, it is unclear whether the reaction occurs toward native nucleic acid bases; however, the combination of the photodimerization pair can be selected freely, in their case. Therefore, the strategy has far-reaching potential for improving the photoreactivity and for regulating the irradiation wavelength required for activating the photoreaction.

7.6 Applications of Photo-Cross-Linking Reaction in Nucleic Acids

The sequence specific photo-cross-linking reaction using various photo-cross-linkers mentioned above is applicable for regulating biological events including nucleic acid, such as replication, transcription, translation, and DNA damage repair, and also DNA nanostructures (Fig. 7.6). As the timing and area of photoirradiation can be regulated completely, the spatiotemporal regulation of the biological events or nanostructures mentioned above is expected to be regulated freely with photoirradiation.

7.6.1 Photoregulation of Gene Expression

The photodynamic antisense strategy (Fig. 7.7a) is a successful example of regulating gene expression in cells. In this strategy, photo-responsive ODNs having complementary sequence of target mRNA specifically cross-link and form irreversible photoadduct with target mRNA. Therefore, the translation of target mRNA is
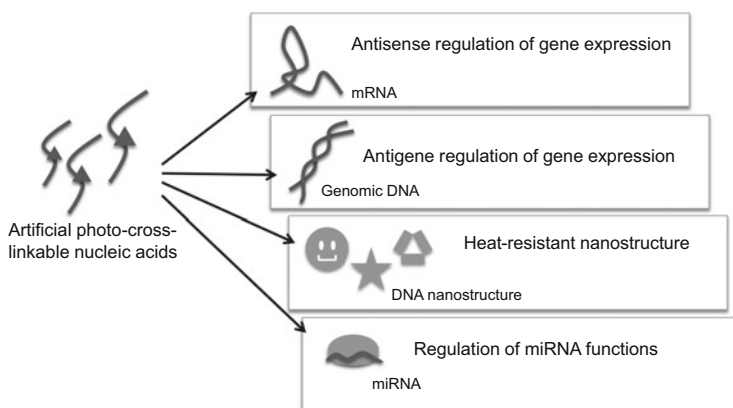

Fig. 7.6 Possible applications of sequence-specific photo-cross-linking reactions using photo-functionalized ODNs
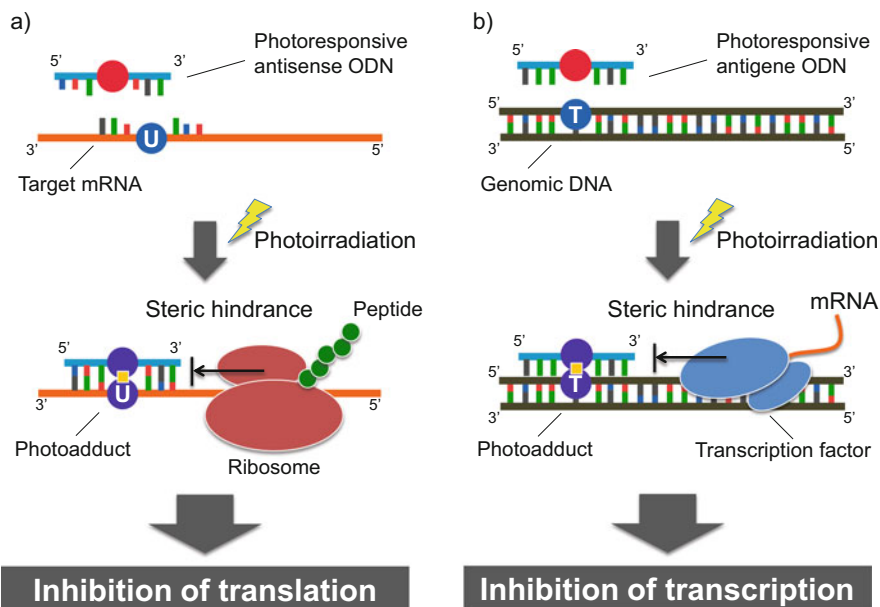
Fig. 7.7 Schematic drawings of photoregulation of gene expression based on (**a**) antisense or (**b**) antigene strategy

selectively inhibited by steric hindrance. The main concept of the photodynamic antisense strategy was advocated by Millar and co-workers as mentioned above [21]. They successfully demonstrated that trioxsalen-modified antisense ODN effectively downregulates rabbit globin gene expression in an in vitro translation system in a photo-responsive manner. In an early report of the cellular application of trioxsalen-modified antisense ODN, Chang et al. and Lin et al. successfully photo-regulated the translation of point-mutated ras protein in 453 cells [22] and collagenase I in dermal fibroblast [23], respectively. Murakami's group of KIT energetically worked in this area [45, 46], and they successfully demonstrated that trioxsalen-modified antisense ODN effectively regulates the gene expression of HPV E6 and E7 mRNA and suppresses the proliferation of HPV positive SiHa cells with nanomolar treatment of trioxsalen-modified antisense ODN and UVA irradiation. Recently, the temporal regulation of constitutive GFP gene expression has been demonstrated by the use of ^{CNV}K-modified antisense ODNs [47]. The high photoreactivity of ^{CNV}K enables quick regulation of gene expression in cells with 10 s of UVA irradiation.

As another strategy for regulating gene expression in a photo-responsive manner, the photodynamic antigene strategy (Fig. 7.7b) has been reported by several researchers. Psoralen-modified triplex forming ODNs is one of the successful examples of this strategy. The ODNs are effective for regulating gene expression with sequence specific photo-cross-linking reaction between the psoralen moiety tethered with ODN and double-stranded genomic DNA. Based on this strategy, the

downregulation of interleukin 2 receptor [27], human rhodopsin [48], and β-globin [49] genes in cells has been reported.

### 7.6.2   Photo-Cross-Linking Reaction for Nucleic Acids Analysis

Because of the highly thermal stability of the photo-cross-linked duplexes, photoreactive synthetic ODNs are applicable for highly sensitive detection of nucleic acids or as a nucleic acid capture probe.

The reactivity of the photo-cross-linking reaction through [2 + 2] photocycloaddition is quite different among pyrimidine bases. Using this character, 5-methyl modification of cytosine in the DNA strand was clearly discriminated with unmodified cytosine by the use of psoralen- or ^{CNV}K-modified ODN probes (Fig. 7.8 [50, 51]). Based on this selective photo-cross-linking reaction, the methodology for analyzing epigenetic modification of DNA can be further developed.
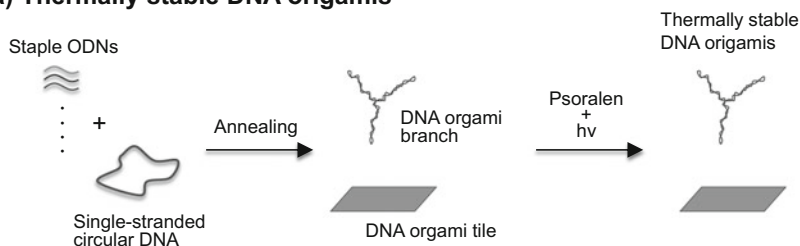
7.6.3   Photo-Cross-Linking Reaction for Nanotechnology

DNA-based nanotechnologies, such as DNA nanocrystal and DNA origami, are cutting-edge areas in nanotechnology and supramolecular science. The bottom-up manner of this technology, which relies on the simple hybridization property of DNA strands, is expected to lead to the construction of various nanostructures and functions induced by finely designed nanostructures. DNA photo-cross-linking is applicable also in this area. The thermally stable double-stranded DNA caused by the interstrand photo-cross-linking reaction of psoralen gives thermally stable
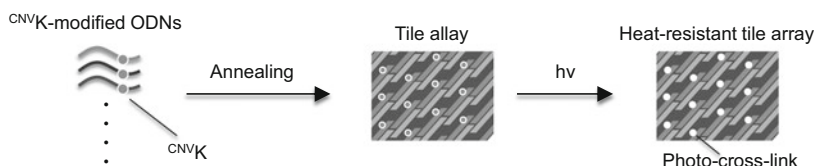

Fig. 7.8 Selective photo-cross-linking of psoralen or ^{CNV}K-modified ODN with 5-methylcytosine
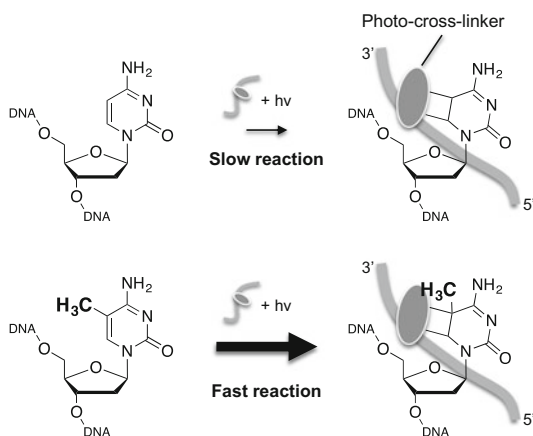
a) Thermally stable DNA origamis

b) Thermally stable ODN tile array

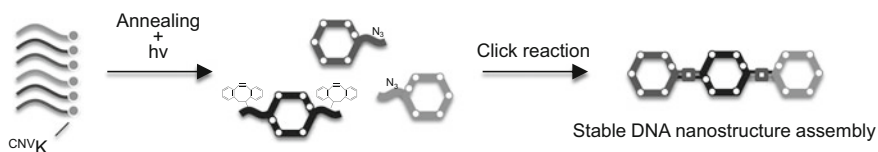## c) DNA nanostructure assembly

Fig. 7.9 Schematic drawings of thermally stable nanostructure with DNA photo-cross-linking reaction. (**a**) Thermally stable DNA origamis. (**b**) Thermally stable ODN tile array. (**c**) DNA nanostructure assembly

nanostructured DNA (Fig. 7.9a), such as DNA origami tiles [52], DNA origami branches [53], and branched oligonucleotide networks [54]. The ability to use these nanostructures at higher temperature enables various applications such as the creation of nanoscale electronic devices and higher-temperature assembly of functional molecules on nanostructured DNA. ^{CNV}K-modified ODNs are also applicable for constructing thermally stable DNA nanostructures. Tagawa et al. and Nakamura et al. reported that the DNA double-crossover AB-staggered tiles having ^{CNV}K and DNA 2D array including ^{CNV}K, respectively, could be stabilized by UVA irradiation (Fig. 7.9b [55, 56]). Furthermore, Gerrard et al. successfully developed a method of integrating nanostructured DNA using thermally stable nanostructured DNA modules and orthogonal copper-free click chemistry (Fig. 7.9c [57]). Since the thermal stability of nanostructured DNA is an important issue for constructing higher-ordered DNA nanostructures, the photo-cross-linking strategies mentioned above are expected to contribute to the further development of DNA-based nanotechnology.

Most recently, Kanaras's group of the University of Southampton successfully demonstrated that the assembly of nanoparticles is finely and reversibly regulated

by the irradiation of UV light [58]. They used 15 nm two gold particles modified with only one DNA strand, one has ^{CNV}K and one has a thymine base as the photo-cross-linking site, and clearly demonstrated that the dimer assembly and dis-assembly were completely regulated by 365 and 312 nm irradiation, respectively. Since the triangle and tetrahedron structure, which has gold nanoparticles at its vertexes and photo-cross-linked duplexes at its sides, is also assembled by using a similar strategy, this new technique will be of particular applicability in several research fields using nanoparticle assemblies such as catalysis, photonics, and biosensors.

7.7   Conclusion and Prospects

Functionalized ODNs having photo-cross-linking ability possess great potential for regulating functions and structures of nucleic acids because of their sequence selectivity, thermally irreversibleness, and photo-responsive manner.

However, problems still remain with the clinical application of photo-cross-linking ODNs, e.g., the cytotoxicity of photoreactive moieties, unexpected photodamage caused by UVA [59], and low transparency of UVA in bio-organs. Further development of photoreactive groups having photo-cross-linking ability with longer wavelengths and low cytotoxicity is required and also a combination with advanced light sources such as femtosecond pulse lasers that can activate molecules by two or three photons with longer wavelengths.

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