Adhesive Surfaces

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Photoinduced Bioorthogonal 1,3-Dipolar Poly-cycloaddition Promoted by Oxyanionic Substrates for Spatiotemporal Operation of Molecular Glues

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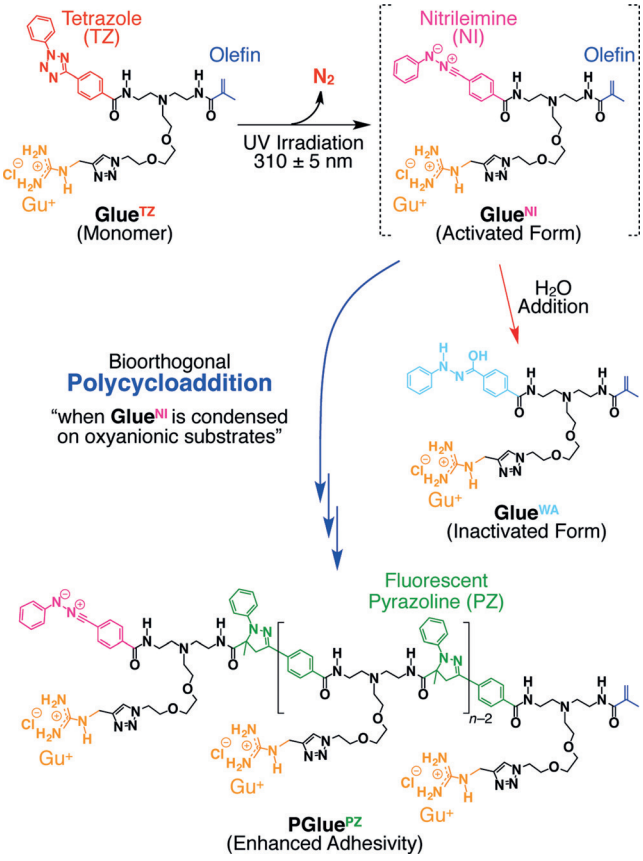
Abstract: *PGlue^{PZ}, a pyrazoline (PZ)-based fluorescent adhesive which can be generated spatiotemporally in living systems, was developed. Since PGlue^{PZ} carries many guanidinium ion (Gu$^+$) pendants, it strongly adheres to various oxyanionic substrates through a multivalent salt-bridge interaction. PGlue^{PZ} is given by bioorthogonal photopolymerization of a Gu$^+$-appended monomer (Glue^{TZ}), bearing tetrazole (TZ) and olefinic termini. Upon exposure to UV light, Glue^{TZ} transforms into a nitrileimine (NI) intermediate (Glue^{NI}), which is eligible for 1,3-dipolar polycycloaddition. However, Glue^{NI} in aqueous media can concomitantly be deactivated into Glue^{WA} by the addition of water, and the polymerization hardly occurs unless Glue^{NI} is concentrated. We found that, even under high dilution, Glue^{NI} is concentrated on oxyanionic substrates to a sufficient level for the polymerization, so that their surfaces can be point-specifically functionalized with PGlue^{PZ} by the use of a focused beam of UV light.*

Adhesion is an interfacial phenomenon of universal importance in our daily life, and a variety of adhesives or glues are now available.[1] Such materials usually implement a mechanism to enhance their interfacial adhesivity in response to certain stimuli, such as heat and light.[1] Light especially, is an attractive trigger for point-specific operations, since it can spatiotemporally control a variety of events.[2] Therefore, photocurable adhesives have been developed not only for the precision assembly of industrial devices[3] but also for medical applications such as dental restoration and wound closure.[4] We envision that an adhesive which is point-specifically photocurable in living systems would possibly manipulate biological events in a spatiotemporal manner.

Herein we report PGlue^{PZ} (Scheme 1) as a conceptually new adhesive which can fully address the above request. Since PGlue^{PZ} carries many guanidinium ion (Gu$^+$) pendants, it strongly adheres to oxyanionic substrates such as silica, latex nanoparticles, DNA, and living cells, through a multivalent Gu$^+$/oxyanion salt-bridge interaction.[5] As shown in Scheme 1, PGlue^{PZ} can be prepared by the photopolymerization of a Gu$^+$-appended water-soluble monomer (Glue^{TZ}) bearing 2,5-diphenyltetrazole (TZ) and olefinic termini. Upon exposure to UV light, Glue^{TZ} transforms into a reactive nitrileimine (NI) intermediate (Glue^{NI}; black arrow), which is eligible for 1,3-dipolar poly-cycloaddition (blue arrows). The elementary reaction of this polymerization has been reported to proceed bioorthogonally in living systems.[6–8] Barner-Kowollik and co-workers reported that this reaction can be utilized for site-specific surface modification of various



Scheme 1. A guanidinium ion (Gu$^+$)-appended water-soluble monomer (Glue^{TZ}) carrying tetrazole (TZ) and olefinic termini, and its photochemical transformation into a nitrileimine-based reactive intermediate (Glue^{NI}) with elimination of N_2, followed by bioorthogonal 1,3-dipolar polycycloaddition, thus affording a pyrazoline (PZ)-based fluorescent polymer (PGlue^{PZ}) carrying multiple Gu$^+$ pendants for enhanced adhesion toward oxyanionic substrates. Without oxyanionic substrates under high dilution, Glue^{NI} preferentially reacts with water and is inactivated in the form of Glue^{WA}.

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substrates.[9] They also reported that photoinduced polycondensation of bifunctional monomers, bearing TZ and olefin units, is possible in organic solvents.[10] However, Glue^{NI} in aqueous media can concomitantly be deactivated into Glue^{WA} by the addition of water (red arrow).[8] Because of this essential side reaction, the polymerization of Glue^{NI} hardly occurs unless Glue^{NI} is concentrated. In the present work, we found that, even under high dilution, Glue^{NI} can be concentrated, though dynamically, through a monovalent salt-bridge interaction on oxyanionic surfaces, to a sufficient level for the polymerization (Figure 1a).[11] By virtue of this, the use of a focused beam of UV light allows spatiotemporal functionalization of oxyanionic substrates, including biological polymers with PGlue^{PZ}. Namely, PGlue^{PZ} serves as a molecular glue which can form and operate spatiotemporally in biological systems. In 2009, we developed the basic design of "molecular glues"[12] carrying multiple Gu$^+$ pendants which adhere tightly to the oxyanionic surfaces of biological macromolecules through a multivalent Gu$^+$/oxyanion salt-bridge interaction. This strategy may provide a variety of interesting possibilities. For example, one of our molecular glues strongly adheres to microtubules and suppresses its depolymerization by gluing together the constituent tubulin proteins, just as paclitaxel does.[12a] So, molecular glues may be useful for pharmacological applications. Despite such a large potential, one has to consider that the molecular glues reported thus far do not provide any target specificity because oxyanionic substrates exist ubiquitously in biological systems. The new strategy presented in Scheme 1 allows molecular glues to form and operate point-specifically, and would solve this essential problem.

Glue^{TZ} was synthesized according to the procedures described in the Supporting Information and characterized unambiguously using a variety of analytical methods.[13] As a proof-of-concept study for Scheme 1, we attempted photopolymerization of Glue^{TZ} using silica as a representative oxyanionic substrate. Thus, a silica plate was dipped in a Tris-HCl (20 mM, pH 8.5) buffer solution of Glue^{TZ} (1 mM) and exposed to UV light ($\lambda = 310 \pm 5$ nm, 100 W) point-specifically for 2 minutes (Figure 1b), wherein only an exposed area turned light-emissive in green (Figure 1c). Meanwhile, when a Tris-HCl (20 mM, pH 8.5) buffer solution of Glue^{TZ} (1 mM) containing silica particles ($\Phi = 40$–50 μm, 25 mg mL^{-1}) was illuminated with UV light for 2 minutes, only the silica particles became emissive (Figure 1d). In contrast, no emission emerged from silica when it was added after the solution of Glue^{TZ} was irradiated with UV light for 2 minutes. As shown in Scheme 1, Glue^{TZ} under UV irradiation is converted into Glue^{NI} (black arrow), which is eligible for the poly-cycloaddition (blue arrows). However, under such high-dilution conditions (1 mM), deactivation of Glue^{NI} into Glue^{WA} by the addition of water (red arrow) occurs preferentially over the poly-cycloaddition reaction (blue arrows). In contrast, when an oxyanionic substrate such as silica is present, Glue^{NI} (Glue^{TZ}) is condensed dynamically on its surface by the Gu$^+$/oxyanion salt-bridge interaction and therefore can be polymerized (Figure 1a). Produced PGlue^{PZ} is multivalent and adheres to the oxyanionic surface tightly (Figure 1c and d). To support these hypotheses, we tried to isolate the products formed on the silica plate in Figure 1c by incubation for 1 hour in aqueous NaOH and subsequent extraction with MeOH. Although a part of PGlue^{PZ} remained

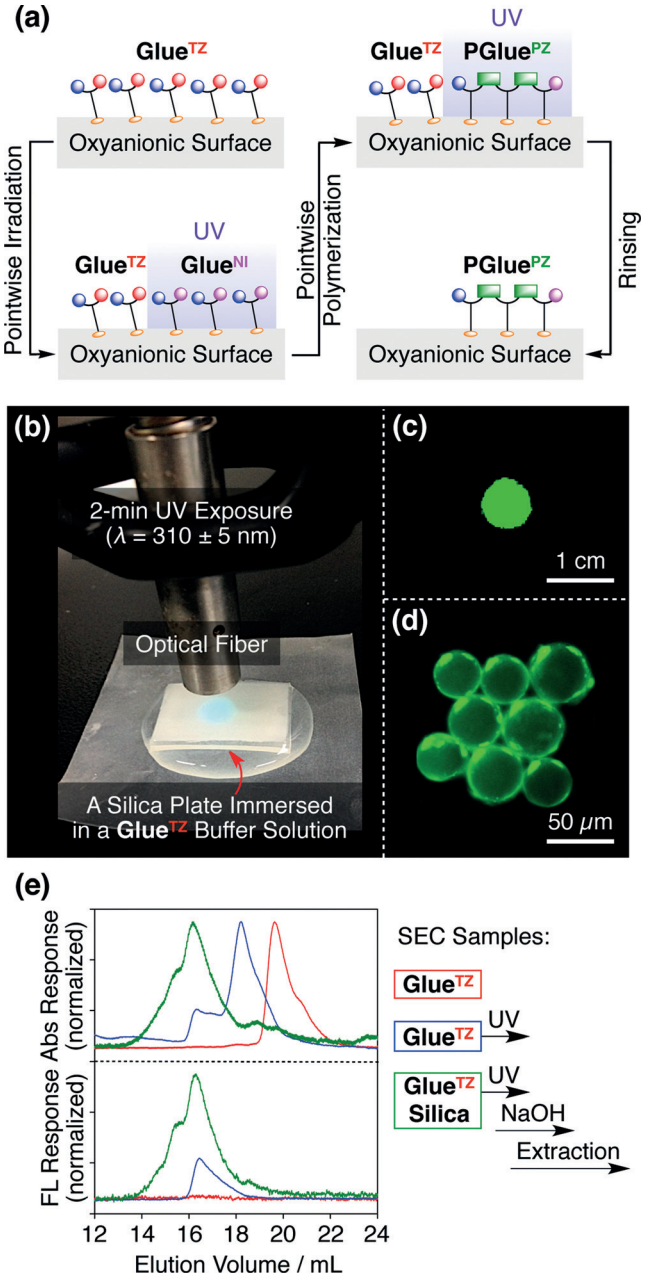

Figure 1. a) Schematic illustration of the mechanism of spatiotemporal photopolymerization of Glue^{TZ}. b–e) Photopolymerization of Glue^{TZ} (1 mM) in Tris-HCl (20 mM, pH 8.5) buffer on silica upon 2 min exposure of UV light ($\lambda = 310 \pm 5$ nm, 100 W). b) An experimental setup for the photopolymerization using a focused beam of UV light. c) A fluorescence micrograph of the silica plate point-specifically exposed to UV light for 2 min in the solution of Glue^{TZ} using the experimental setup shown in (b). d) A fluorescence micrograph of silica particles after 2 min UV exposure in the solution of Glue^{TZ}. e) SEC traces of Glue^{TZ} (red), UV-exposed Glue^{TZ} (blue), and PGlue^{PZ} (green) extracted with MeOH from the UV-exposed silica plate after 1 h incubation in a 1.0 M aqueous solution of NaOH. Normalized absorption ($\lambda = 315$ nm) and fluorescence ($\lambda = 530$ nm/$\lambda_{ext} = 360$ nm) responses.

unextracted, probably because of the highly adhesive nature of long-chain PGlue^{PZ}, a size-exclusion chromatography trace of the MeOH extract (Figure 1e, green) indeed showed a luminescent polymeric fraction at a higher molecular-weight region than the precursor Glue^{TZ} (Figure 1e, red). Its MALDI-TOF mass spectral profile displayed oligomeric fractions of PGlue^{PZ} with lengths of up to the hexamer (see Figure S7 in the Supporting Information).[13] In contrast, without silica, some dimeric species, together with the water adduct of Glue^{NI} (Glue^{WA} in Scheme 1), were observed in Figure 1e (blue) as the main products (see Figure S6 in the Supporting Information).[13] By using fluorescence microscopy and X-ray photoelectron spectroscopy (see Figures S8 and S9 in the Supporting Information),[13] we confirmed that the monomer Glue^{TZ} can be removed by rinsing, whereas PGlue^{PZ} stays on the silica plate even after multiple rinses (Figure 1a).

Analogous to silica, latex nanoparticles with surface CO_2^- anions (LTX$^-$) promote the polymerization of Glue^{NI} (Figure 2a, red). When an aqueous solution of Glue^{TZ} (10 μM) containing LTX$^-$ ($\Phi \approx 100$ nm, 1.25 mg mL^{-1}; [CO_2^-] = 5 μM) was exposed to UV light ($\lambda = 310 \pm 5$ nm, 100 W), an intense emission at $\lambda = 490$ nm, which is assignable to the pyrazoline fluorescence, emerged upon excitation at $\lambda = 360$ nm (Figure 2a, green).[8] The fluorescence quantum yield of the solution was 38% (see Table S1 in the Supporting Information).[13] As expected, when positively charged latex nanoparticles with alkylammonium cations (LTX$^+$; $\Phi = \approx 100$ nm, 1.25 mg mL^{-1}, [NR_3^+] = 5 μM) were used instead of LTX$^-$ under conditions otherwise identical to those above, only a negligibly weak emission appeared at $\lambda = 490$ nm (Figure 2a, orange). As shown in Figure 2b, the use of the rhodamine-containing LTX$^-$ (^{Rhd}LTX$^-$) as an oxyanionic substrate resulted in the occurrence of fluorescence resonance energy transfer (FRET) between rhodamine and PGlue^{PZ}. Namely, PGlue^{PZ} is attached to the oxyanionic surface of ^{Rhd}LTX$^-$ in the reaction medium. In the absence of LTX$^-$ under conditions otherwise identical to those above (Figure 2a, blue), no appreciable increase in fluorescence intensity resulted. The same held true when LTX$^-$ was added after the photoirradiation, thus indicating a short lifetime of Glue^{NI} in aqueous media (Figure 2c, blue). When the system containing 0.025 mg mL^{-1} of LTX$^-$ was exposed to UV light, the fluorescence intensity resulting from PGlue^{PZ} emerged abruptly in the initial stage and then reached a plateau after 30 seconds (Figure 2c, green). Upon incremental increases in the amount of LTX$^-$, up to 0.4 mg mL^{-1}, the fluorescence was intensified (Figure 2c and d). After this inflection point, the amount of LTX$^-$ seemed to be too much for a given [Glue^{NI}] in this experiment (Figure 2c and d).

DNA having multiple phosphate anions (PO_4^-) can also serve as an oxyanionic promoter for the photopolymerization of Glue^{TZ}. Figure 3a shows an electrophoretic migration profile of a linearized plasmid DNA sample (pUC19; 2686 bp, [Gu^+]/[PO_4^-] = 0) in agarose gel. When this sample was mixed with Glue^{TZ} at [Gu^+]/[PO_4^-] > 5 and then exposed to UV light for 2 minutes, no electrophoretic migration was observed (Figure 3b). This result indicates that PGlue^{PZ} produced by the photopolymerization of Glue^{NI} on the DNA strand

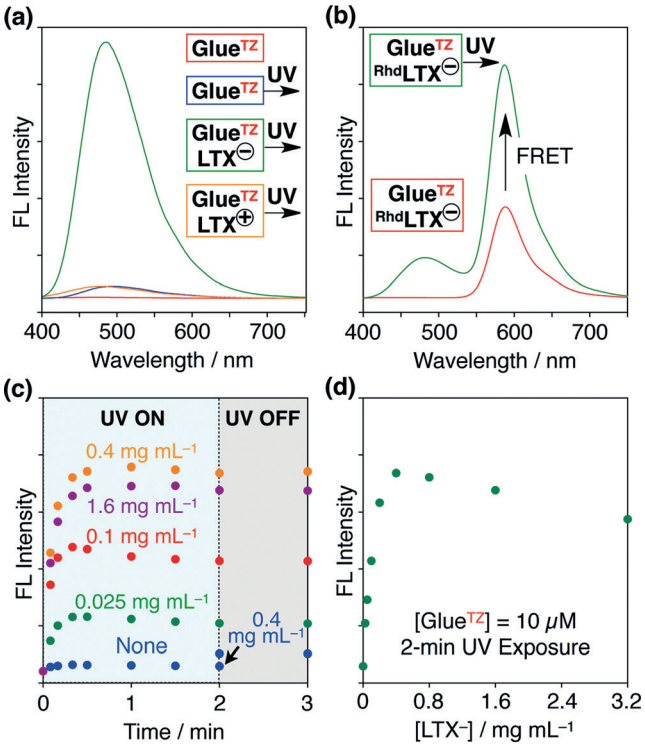

Figure 2. Photopolymerization of Glue^{TZ} (10 μM) in the absence and presence of oxyanionic substrates in Tris-HCl (20 mM, pH 8.5) buffer upon exposure to UV light ($\lambda = 310 \pm 5$ nm, 100 W). a) Fluorescence spectra ($\lambda_{ext} = 360$ nm) before (red) and after 2 min UV exposure in the absence (blue) and presence of oxyanionic (LTX$^-$; 1.25 mg mL^{-1}, green) and cationic (LTX$^+$; 1.25 mg mL^{-1}, orange) latex nanoparticles. b) Fluorescence spectra ($\lambda_{ext} = 360$ nm) of rhodamine-containing LTX$^-$ (^{Rhd}LTX$^-$) before (red) and after 2 min UV exposure (green). c) Time profiles of the fluorescence intensity changes ($\lambda_{em} = 490$ nm) upon UV exposure (0–2 min) in the absence (blue) and presence (green, red, orange, and purple) of LTX$^-$ (0.025, 0.1, 0.4, and 1.6 mg mL^{-1}, respectively). LTX$^-$ (0.4 mg mL^{-1}) was added after 2 min UV exposure (blue). d) Fluorescence intensity ($\lambda_{em} = 490$ nm) after 2 min UV exposure in the presence of LTX$^-$ (0–3.2 mg mL^{-1}).

strongly adhered to this oxyanionic substrate and effectively neutralized its negative charges. In contrast, without UV exposure under conditions otherwise identical to those above, Glue^{TZ} did not affect the DNA migration (Figure 3a) even at [Gu^+]/[PO_4^-] = 25. Meanwhile, Glue^{TZ}, pre-exposed to UV light for 2 minutes before being mixed with DNA, hardly retarded the electrophoretic migration of the DNA (Figure 3c). This result is reasonable considering the short lifetime of Glue^{NI} in aqueous media (see above).

Having these observations in mind, we investigated the possibility of point-specific modification of biological macromolecular motifs with PGlue^{PZ} using a focused beam of UV light. For this purpose, we used a DNA-immobilized plastic plate, where DNA was covalently attached, to the areas marked [i]–[iii] (Figure 4a), by the reaction of mono-NH_2-ended DNA (100 bp) with active ester units prefunctionalized on the surface. After the immobilization reaction, the plastic plate was rinsed successively with 0.5 M aqueous NaOH and water for the removal of the unreacted DNA and hydrolysis of the active ester units. Then, an aqueous solution of Glue^{TZ}

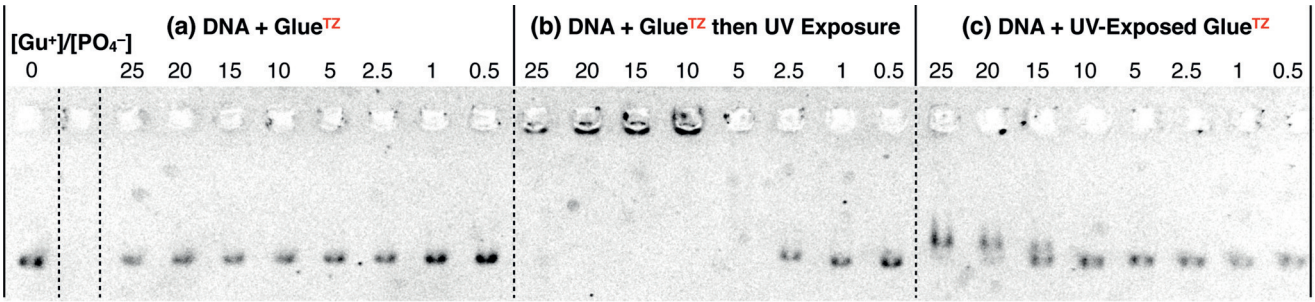

Figure 3. Agarose gel electrophoresis profiles of linearized plasmid DNA (pUC19) with Glue^{TZ} before (a)and after 2 min UV exposure (b; $\lambda = 310 \pm 5$ nm), and with UV-exposed Glue^{TZ} (c). Samples were prepared at $[Gu^+]/[PO_4^-] = 0$–25 and placed on an agarose gel which was subsequently stained with SYBR Green I for fluorescently visualizing the electrophoresis profiles upon excitation at $\lambda = 470$ nm.

(10 μM) was introduced as a droplet on the plastic plate, in such a way that the droplet covered the spots [i], [ii], and [iv] (Figure 4a, orange circle). Then, the spots [i], [iii], and [iv] (purple circles) were point-specifically exposed to a focused beam of UV light ($\lambda = 310 \pm 5$ nm, 100 W) for 2 minutes (Figure 4a), and then the plate was rinsed thoroughly with water. When this modified plate was illuminated entirely at $\lambda = 365$ nm (Figure 4b–d), only spot [i] showed a blue emission resulting from PGlue^{PZ}, whereas no other spots fluoresced. Thus, by the use of a focused beam of UV light, only the light-exposed area of the DNA surface was point-specifically functionalized with PGlue^{PZ}. This polymer carries many Gu^+ pendants and tightly adheres to oxyanionic substrates. Therefore, regardless of whether the plate is located in air or immersed in aqueous media, PGlue^{PZ}, point-specifically generated, does not migrate to other areas. Next, we considered the fate of Glue^{NI} generated for spot [iv]. DNA is not immobilized in spot [iv]. Hence, Glue^{NI} photochemically generated at spot [iv] has the potential to diffuse to DNA-immobilized spot [ii] and polymerize therein. However, no fluorescence emission resulted from spot [ii]. This observation indicates a possibility that Glue^{NI} is deactivated before diffusion to spot [ii] by the addition of water (Scheme 1, red arrow) as soon as it is generated at spot [iv].

The successful results of DNA-promoted photopolymerization of Glue^{TZ} prompted us to extend the scope of this bioorthogonal photopolymerization toward cellular systems (Figure 5). Thus, human hepatocellular carcinoma Hep3B cells (1.0×10^4 cells well^{-1}, Figure S16)[13] were humidified for 24 hours at 37 °C with 5 % CO_2 in an Eagle's minimal essential medium (EMEM, 200 μL) containing Glue^{TZ} (0.5 mM). When the resultant incubation mixture was exposed to UV light ($\lambda = 310 \pm 5$ nm, 100 W) for 2 minutes and subjected to confocal laser-scanning microscopy upon two-photon excitation at $\lambda = 720$ nm, the cells emitted strong fluorescence derived from pyrazoline in the cell interior (Figure 5a and Figure S17 in the Supporting Information).[13] Namely, even in the cellular environment, the photopolymerization of Glue^{TZ} can be promoted by cellular oxyanionic substrates. The fluorescence activity mostly remained intact during the rinsing treatment with Dulbecco's PBS (D-PBS, 100 μL × 2; Figure 5b). In contrast, when the mixture was first rinsed with D-PBS (200 μL × 2) and then exposed to UV light, only a negligibly weak fluorescence emission emerged (Figure 5c). These

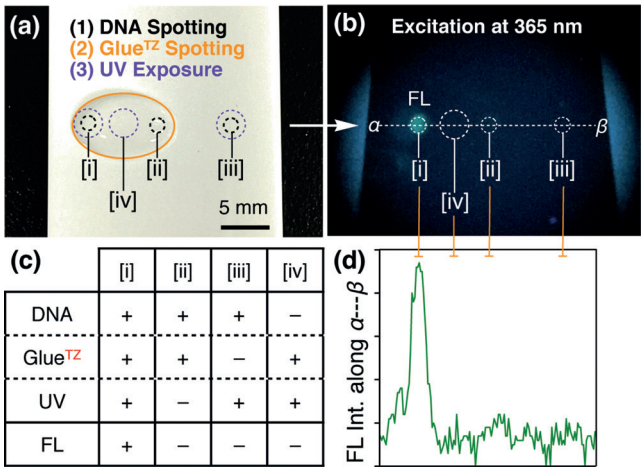

Figure 4. Photopolymerization of Glue^{TZ} on a DNA-immobilized substrate. a) Immobilization of DNA, bearing an NH_2 terminus (100 bp), onto an active ester-functionalized plastic substrate at spots [i]–[iii]. After rinsing with 0.5 M NaOH and water, the substrate was immersed in a Tris-HCl (20 mM, pH 8.5) buffer solution of Glue^{TZ} (10 μM, inside orange circle). Then, the substrate was exposed to focused UV light ($\lambda = 310 \pm 5$ nm) for 2 min (inside purple dashed circles), followed by rinse with water. b) An image of the resultant substrate under $\lambda = 365$ nm UV illumination. c) The experimental conditions and fluorescence response of spots [i]–[iv]. d) Fluorescence intensity along the white dashed line between α and β in (b) evaluated by using ImageJ software.

contrasting results indicate that multivalent PGlue^{PZ} tightly adheres to cellular oxyanionic components, whereas weakly adhesive monovalent Glue^{TZ} is removed by the rinsing treatment. Moreover, we found that this highly adhesive PGlue^{PZ} causes cell death. The viability of Hep3B cells was evaluated by CellTiter-Glo assay. Glue^{TZ}-containing EMEM (100 μL) was added to Hep3B cells (5.0×10^3 cells well^{-1}), and the mixture was subsequently incubated for 2 minutes under UV exposure. The medium was replaced with fresh Glue^{TZ}-free EMEM (100 μL), and the mixture was incubated at 37 °C for 24 hours and then subjected to the viability assay. As shown in Figure 5d (green), cell death was induced when the [Glue^{TZ}] was greater than 0.1 mM, and the cell viability dropped to less than 50 % at [Glue^{TZ}] = 0.5 mM. In contrast, neither the use of Glue^{TZ} without UV exposure (Figure 5d,

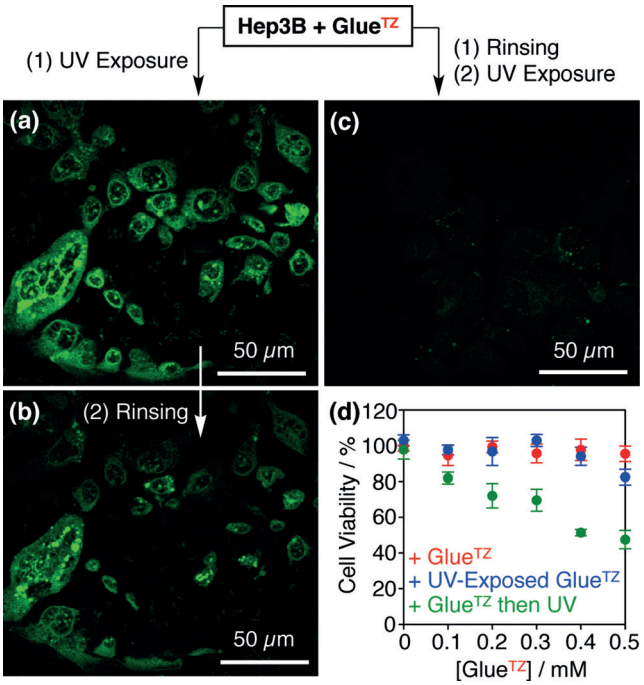

Figure 5. Confocal laser scanning microscopy upon two-photon excitation at $\lambda = 720$ nm of Hep3B cells (1.0×10^4 cells well^{-1}) after incubation at 37 °C for 24 h in EMEM (200 μL) containing Glue^{TZ} (0.5 mM). Fluorescence micrographs taken after 2 min UV exposure (a; $\lambda = 310 \pm 5$ nm, 100 W) followed by rinsing with D-PBS (200 μL × 2) and subsequent incubation at 37 °C for 24 h in EMEM (b; 200 μL), or after rinsing with D-PBS (200 μL × 2) and subsequent incubation at 37 °C for 24 h in EMEM (200 μL) followed by 2 min UV exposure (c). d) Viability profiles of Hep3B cells (5.0×10^3 cells well^{-1}) using the CellTiter-Glo assay. For sample preparation, Hep3B cells were incubated for 2 min in EMEM (100 μL) containing Glue^{TZ} (0–0.5 mM) without (red) and with (green) UV exposure or likewise incubated in EMEM (100 μL) containing UV-exposed Glue^{TZ} (0–0.5 mM; blue). Prior to the viability assay, all samples thus obtained were further incubated at 37 °C for 24 h in EMEM (100 μL).

blue) nor Glue^{TZ} treated beforehand by 2 minutes of UV exposure in EMEM (100 μL; Figure 5d, red) resulted in lowering the cell viability. As shown in Figure 5d (green; [Glue^{TZ}] = 0 mM), UV exposure of the cells for 2 minutes in the absence of Glue^{TZ} hardly resulted in the cell death. Therefore, highly adhesive PGlue^{PZ} plays a critical role in deteriorating the cells.

In conclusion, we successfully developed novel bioorthogonal photopolymerization (Scheme 1) which allows spatiotemporal surface functionalization of oxyanionic substrates such as DNA and living cells, as well as silica and latex nanoparticles, with the fluorescent polymeric molecular glue PGlue^{PZ} by using a focused beam of UV light. The results reported herein, including cell viability testing, indicate that highly adhesive PGlue^{PZ}, generated by this top-down photochemical approach, can selectively stain target tissues and modulate their biological functions, although PGlue^{PZ} intrinsically is not tissue-selective. Pharmacological studies using drug-appended Glue^{TZ} and PGlue^{PZ} is one of the interesting subjects worthy of further investigation.

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nanoparticle and DNA upon titration with Glue^{TZ} (see the Supporting Information).

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