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Proximity-Activated Photocatalytic Pharmacology: From Subcellular Compartments to Neural Circuits

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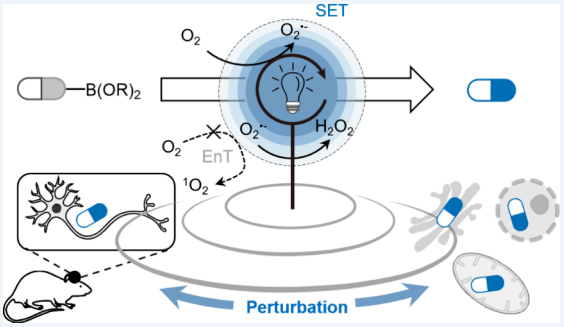
CONSPECTUS: Spatial precision of endogenous biological signaling is dictated by submicrometer microdomains. Traditional pharmacological modalities lack spatial resolution needed to interrogate discrete coordinates, whereas genetic methods often lack rapid kinetic control needed to capture dynamic signaling networks. While photochemical tools offer noninvasive, spatiotemporally resolved control, their biological translation is limited by UV phototoxicity, nonspecific ROS damage, and the difficulty to achieve true subcellular localization.



We summarize our development of proximity-activated photocatalytic pharmacology via spatially confined small-molecule release, focusing on mechanistic evolution of biocompatible, metal-free photocatalytic deboronative hydroxylation of organoboronates. We present a paradigm where reaction fidelity is governed not by intrinsic photochemical properties of substrates but by physical coordinates of the localized photocatalyst and short-lived reactive species generated within defined spatial boundaries. This platform operates through localized generation of transient intermediates, specifically superoxide anions ($O_2^{\cdot-}$) and H_2O_2, whose intracellular diffusion is constrained by native cellular quenching machinery. By exploiting steep concentration gradients of species, we establish a high-resolution reaction sphere for photocatalytic bond cleavage to enable precise interrogation of biological microdomains.

Our research program progressed through three distinct generations to span increasingly complex biological scales:

- First generation (cellular scale): We established a visible-light-driven small-molecule release system using biocompatible organic xanthene dyes and physiological ascorbates. Operating through a single-electron transfer pathway, this manifold selectively reduces molecular oxygen to $O_2^{\cdot-}$ to drive bioorthogonal deboronative hydroxylation while bypassing cytotoxic energy transfer pathways.
- Second generation (subcellular scale): We achieved subcellular precision by engineering targeted chemical scaffolds and hybrid genetically targeted platforms (e.g., SNAP-FL) to restrict photocatalytic activity to specific organelle coordinates. By advancing to fully genetically encoded 12 kDa miniature photoenzymes (miniSOG), we eliminated exogenous chemical catalyst requirements. Together, these methods enabled us to map compartment-specific drug toxicities, drive selective mitochondrial depolarization, and achieve nucleus-specific epitranscriptomic remodeling of m^{6}A RNA methylation.
- Third generation (circuit scale): We deployed these platforms to decipher complex architecture of the mammalian nervous system. By expressing membrane-anchored SNAP-FL at projection-specific synaptic terminals, we achieved optochemical neuromodulation in acute brain slices within seconds. Ultimately, this enabled cell-type-specific photocatalytic pharmacology *in vivo*, facilitating the selective release of GABA$_B$R agonists within Na$_V$1.8$^+$ terminals to functionally delineate peripheral neural circuits driving pruritus in mice.

By transitioning from bulk cellular activation to localized, genetically directed modulation, we provide a unified mechanistic framework that demonstrates how photocatalyst localization and confined reactive species dynamics dictate complex biological outcomes across multiple spatiotemporal scales.

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- Wang, H.; Li, W.-G.; Zeng, K.; Wu, Y.-J.; Zhang, Y.; Xu, T.-L.; Chen, Y. Photocatalysis Enables Visible-Light Uncaging of Bioactive Molecules in Live Cells. *Angew. Chem. Int. Ed.* **2019**, *58*, 561−565.[1] This study established the first visible-light-driven deboronative hydroxylation in live cells including primary neuron samples using organic dyes, demonstrating that an electron-transfer pathway

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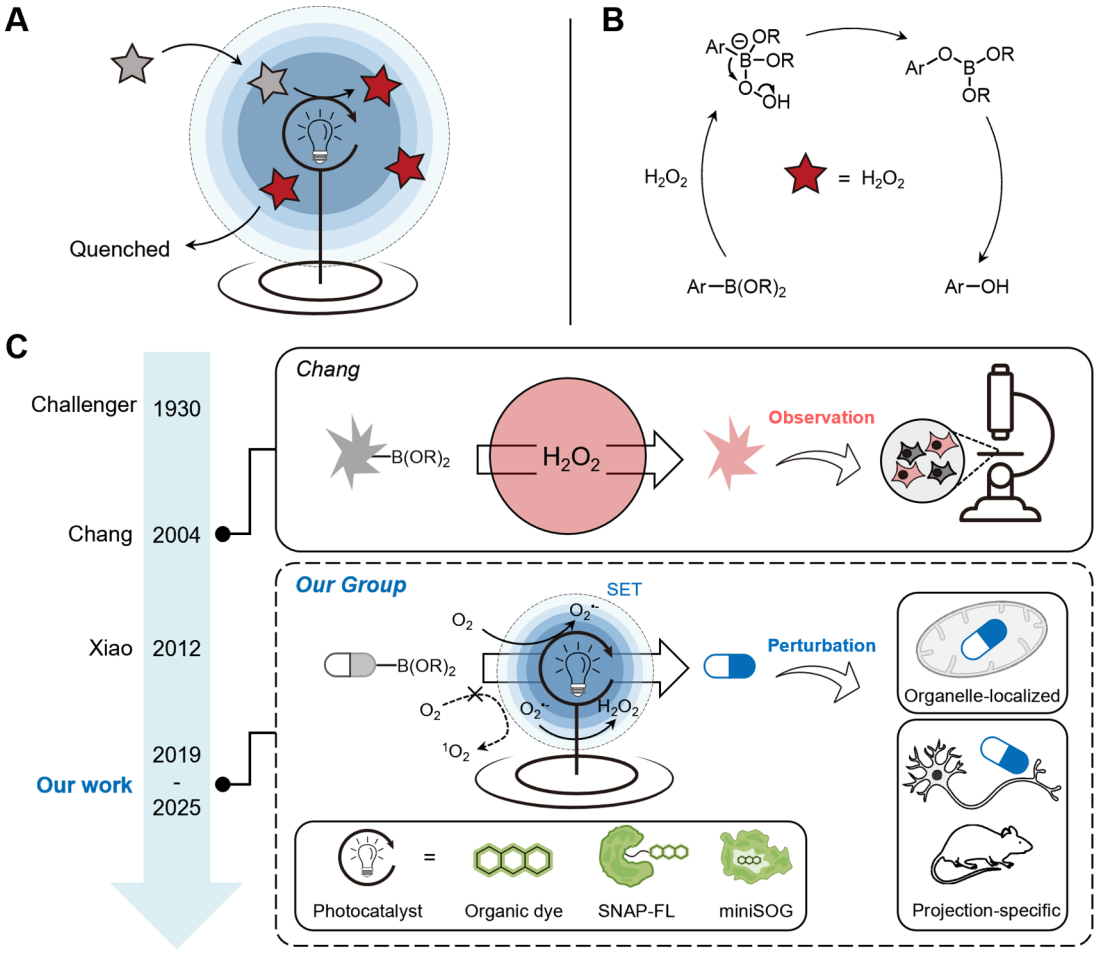

Figure 1. Conceptual, mechanistic, and chronological development of proximity-activated photocatalytic pharmacology. (A) The proximity-activated paradigm: Schematic depiction of how localized photocatalyst activity confines chemical transformations to a submicrometer reaction sphere, enabling the selective activation of expanded biological toolkits while preventing systemic off-target effects. (B) Chemical mechanism: The fundamental pathway of deboronative hydroxylation, proceeding via nucleophilic attack on an organoboron center to form a transient tetracoordinated boronate intermediate, followed by a 1,2-boronate migration and subsequent phenol release. (C) Historical Evolution and Laboratory Trajectory: (left and upper panel) The chronological transition of deboronative hydroxylation from its origins in physical organic chemistry (Challenger), to its application in physiological H_2O_2 sensing (Chang), and its development into visible-light synthetic methodologies (Xiao). (lower panel) Our laboratory's trajectory in advancing spatial resolution from bulk cellular validation via diffuse organic dyes (First Generation), to the high-precision interrogation of subcellular organelle coordinates via targeted hybrid platforms and fully genetically encoded miniature photoenzymes (Second Generation), culminating in projection-specific and cell-type-specific neuromodulation in live neural networks (Third Generation). The Proximity-Activated Zone (PAZ) is maintained by driving a biocompatible SET pathway that generates short-lived $O_2^{\bullet-}$ and H_2O_2 intermediates while bypassing cytotoxic $^1O_2$, ensuring high aerobic compatibility and minimal baseline perturbation.

enables biocompatible bond cleavage without singlet-oxygen-related toxicity.

- Zeng, K.; Jiao, Z.-H.; Jiang, Q.; He, R.; Zhang, Y.; Li, W.-G.; Xu, T.-L.; Chen, Y. Genetically Encoded Photocatalysis Enables Spatially Restricted Optochemical Modulation of Neurons in Live Mice. *ACS Cent. Sci.* **2024**, *10*, 163−175.[2] This work introduced a genetically encoded hybrid photocatalytic platform (SNAP-FL) for organelle-specific drug delivery and achieved the first instance of photocatalytic neuromodulation in live, behaving mice, offering a cell-type-specific, small-molecule alternative to optogenetics.
- Che, Q.; He, R.; Zhang, Y.; Zhang, H.; Zeng, K.; Chen, Y. Miniature Photoenzyme Enables Organelle-Specific Cellular Control via Deboronative Hydroxylation. *Angew. Chem. Int. Ed.* **2025**, *64*, e15137.[3] This paper describes the engineering of a 12 kDa miniature photoenzyme miniSOG for autonomous, high-precision subcellular control and localized nuclear epigenetic remodeling without requiring the delivery of exogenous photocatalysts.

1. INTRODUCTION: THE SPATIOTEMPORAL LOGIC OF PROXIMITY-ACTIVATED PHOTOCATALYTIC PHARMACOLOGY

Deciphering the structural and functional hierarchies of biological signaling requires molecular tools capable of interrogating cellular microdomains with high temporal and submicrometer spatial resolution.[4] While conventional pharmacology offers extraordinary structural diversity, its precision is fundamentally limited by the systemic, unrestricted distribution of small-molecule effectors.[5] Conversely, optogenetics provides impeccable genetic precision but is constrained by the narrow functional repertoire of naturally occurring photosensitive proteins.[6] Photochemistry has emerged as a modular modality

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to bridge this gap, offering light-driven control over small-molecule activation.[7] However, its translation to living systems has been historically hindered by the intrinsic cytotoxicity of high-energy ultraviolet (UV) light and the difficulty of achieving true subcellular resolution via unguided photon irradiation.[8]

To this end, photocatalysis has been introduced to bypass UV-induced phototoxicity by leveraging visible-light-absorbing catalysts to drive bioorthogonal transformations.[9] Yet, the application of photocatalysis within complex biological environments introduces its own fundamental challenge, historically constrained by the physical laws of mass transport. In the homogeneous environment of a synthetic flask, rapid molecular diffusion is a prerequisite for reaction efficiency; in the heterogeneous architecture of a living cell, however, uncontrolled intermediate diffusion leads to severe spatial blurring and nonspecific, off-target macromolecular damage.[10]

To overcome this limitation, several research groups, including our own, have pivoted toward a Proximity-Activated paradigm.[11] The central logic underpinning Proximity-Activated Photocatalysis is that the genetically programmed or chemically targeted localization of a photocatalyst defines the precise coordinates where reactive intermediates are generated.[10,12] Concurrently, the dense endogenous metabolic and quenching machinery of the cell dictates the lifetime and effective diffusion radius of these intermediates, thereby establishing a confined, spherical reactive domain centered precisely on the catalyst (Figure 1A). Any molecular entity residing within this restricted zone—whether endogenous biomacromolecules or artificial small molecules—becomes a potential target for chemical transformation.

While this proximity-dependent logic has been widely adopted in recent years for proximity labeling and interactome profiling,[13] a historical shortage of compatible bioorthogonal bond-cleaving reactions has limited its broader application to targeted pharmacological modulation.[14] We reasoned that a strategy centered on Proximity-Activated Photocatalytic Pharmacology would address this challenge by combining the structural diversity and established multitarget profiles of conventional small-molecule therapeutics with the high spatiotemporal precision afforded by localized photocatalysis. By systematically caging bioactive small molecules to mask their function,[9b,15] these prodrugs remain inert until they encounter the localized photocatalytic sphere. Upon entering this zone, the prodrugs undergo proximity-activated cleavage to release the active drug, minimizing background noise and preventing the spatial blurring caused by systemic diffusion and off-target toxicity.

To realize this strategy, our laboratory developed a bioorthogonal, proximity-activated photocatalytic deboronative hydroxylation manifold using organoboronates.[1,16] This approach traces its intellectual lineage back to the 1930s discovery by Challenger of hydrogen peroxide (H_2O_2)-mediated deboronative hydroxylation[17], a classical organic transformation initiated by peroxide anion attack on an organoboron center, followed by 1,2-boronate migration within a tetracoordinated boronate intermediate to afford the corresponding alcohol (Figure 1B). Consequently, this reactivity was successfully adapted for *in vivo* applications by Chang and co-workers to achieve highly selective H_2O_2 sensing (Figure 1C, upper panel).[18] It was subsequently extended into robust synthetic photocatalytic methodologies by Xiao, Scaiano, and others utilizing superoxide radical anions ($O_2^{\cdot-}$), a transient intermediate sharing a compatible operational profile with H_2O_2 for organoboronate activation.[19] Unlike traditional Type-I photodynamic mechanisms that generate $O_2^{\cdot-}$ via direct electron transfer from an excited catalyst to molecular oxygen,[20] visible-light excitation of these platform triggers a reductive quenching cycle. Here, the photoexcited catalyst is reduced by an exogenous sacrificial reductant to yield a transient photocatalyst radical anion, which subsequently transfers an electron to ground-state molecular oxygen O_2 to generate the primary $O_2^{\cdot-}$ effector.

To transition this reactivity into a targeted bioorthogonal platform, we prioritized a visible-light-driven Single-Electron Transfer (SET) manifold that selectively generates $O_2^{\cdot-}$ and its downstream dismutation product, H_2O_2, thereby bypassing the highly cytotoxic energy transfer (EnT) pathways responsible for producing singlet oxygen ($^1O_2$).[21] By combining this mechanistically privileged catalytic pathway with rapid, native cellular quenching to constrain intermediate diffusion, we successfully established strictly confined, submicrometer reaction volumes at the physical coordinates of the catalyst. Because these SET-generated reactive species possess exceptionally steep intracellular concentration gradients due to the endogenous cellular quenching machinery, the physical coordinates of the photocatalyst dictate the boundaries of a highly localized, submicrometer Proximity-Activated Zone (PAZ) (Figure 1C, lower panel).[22]

This Account explores the evolutionary trajectory of this logic across three generations of spatiotemporal milestones: The First Generation, which established cellular-scale bioorthogonal validation using exogenous organic dyes for cellular uncaging;[1] The Second Generation, which advanced to subcellular microdomain interrogation across diverse organelles (including the nucleus, mitochondria, and endoplasmic reticulum) using hybrid protein-dye fusions (SNAP-FL) and fully genetically encoded 12 kDa miniature photoenzymes (miniSOG);[2,3] The Third Generation, which deployed this spatial fidelity to achieve circuit-level photopharmacology, enabling projection-specific neuromodulation and the cell-type-specific dissection of circuitry in live mice.[2] Through these advancements, we demonstrate how shifting the design priority from substrate structure to the physical coordinates of the catalyst provides a generalizable framework for executing precision biology across hierarchical scales—from subcellular compartments to complex neural circuits.

2. FOUNDATIONAL LOGIC: ESTABLISHING CELLULAR-SCALE BIOORTHOGONAL VALIDATION

The evolution of Proximity-Activated Photocatalytic Pharmacology has unfolded across three distinct spatiotemporal milestones, each representing a strategic reconciliation of catalyst delivery and spatial precision within complex biological environments. As the opening chapter of this trajectory, the First Generation established a robust bioorthogonal chemical blueprint, validating the fundamental reactivity in aqueous test tube conditions using diffuse, exogenous components before progressively migrating toward compartmentalized fusions, fully genetic photoenzymes, and ultimately, circuit-specific *in vivo* live animal architectures. This technological progression has systematically elevated the resolution of light-driven chemical manipulation within living systems.

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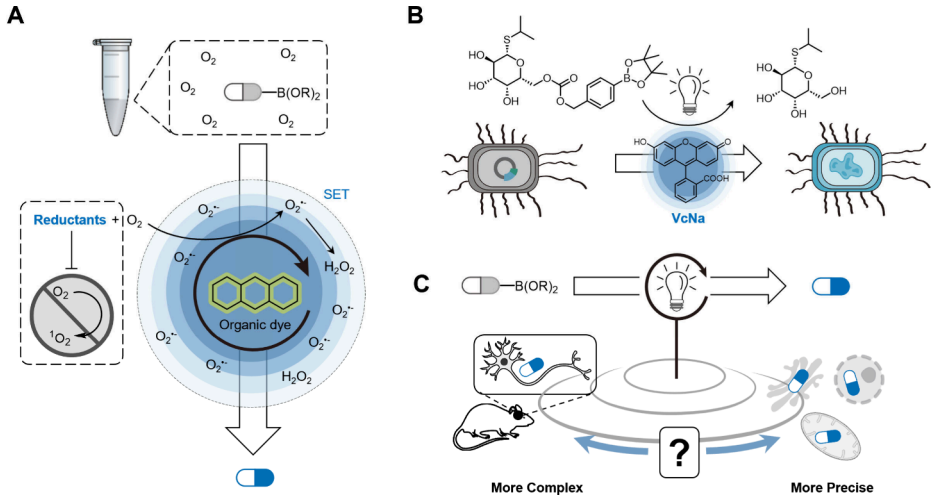

Figure 2. Mechanistic Foundation and Initial Validation of Proximity-Activated Photocatalytic Pharmacology. (A) The biocompatible SET pathway: This SET pathway is validated in neutral aqueous buffer before translation into live mammalian cells, where transient intermediates are safely managed by native antioxidant networks. By bypassing cytotoxic $^1O_2$, this manifold prevents indiscriminate macromolecular damage in both cell-free and intracellular environments. (B) Photocatalytic gene regulation: Visible-light photocatalytic deboronative hydroxylation enables the controlled release of active IPTG containing a free hydroxyl group, driving regulated downstream protein expression in *E. coli* BL21(DE3). (C) The conceptual trajectory toward Photocatalytic Pharmacology: Arrows illustrating the progressive shift from bulk, cellular-scale bioorthogonal uncaging toward subsequent spatiotemporally restricted milestones (subcellular compartments and neural circuits) within increasingly complex biological architectures.

2.1. The Mechanistic Foundation: Single-Electron Transfer (SET)

The foundation of our approach is a biocompatible SET pathway of molecular oxygen that could operate efficiently under aerobic, physiological conditions without inducing detrimental oxidative damage (Figure 2A). Unlike traditional Type II photosensitizers that generate highly toxic singlet oxygen ($^1O_2$) via EnT ($E_T \approx 94$ kJ mol^{-1}),[23] our first-generation systems utilize xanthene-based catalysts—specifically Fluorescein and Rhodamine B, which possess inherently low singlet oxygen quantum yields ($\Phi_\Delta < 0.1$).[24] These photoredox properties enable efficient reductive quenching cycle in neutral aqueous conditions in the presence of physiological reductants like ascorbates.

In this reductive quenching cycle, the photoexcited organic dye undergoes rapid reduction by ascorbate to yield a transient radical anion species. This radical anion dye intermediate subsequently reduces molecular oxygen to a superoxide radical anion ($O_2^{\bullet-}$) ($E_{1/2}^{red} = -0.16$ V vs NHE),[25] which sequentially dismutates or is reduced to yield H_2O_2. When evaluated in cell-free aqueous test tubes, these transient species provide the precise chemical privilege required to selectively trigger the deboronative hydroxylation of organoboronates under mild, neutral conditions.

Translating this chemistry from the controlled environment of an aqueous test tube to an active intracellular matrix introduces immense chemical crowding and competitive metabolic pathways. Because these SET-generated chemical intermediates are endogenous metabolites that participate natively in cellular redox signaling, they are rapidly processed and neutralized by the cell's native antioxidant machinery,[26] minimizing collateral macromolecular damage compared to singlet oxygen.

Quantitatively, Fluorescein and Rhodamine B maintain >90% cell viability in MCF-7 cells after 60 min of continuous irradiation, whereas standard photosensitizers such as Eosin Y and Methylene Blue ($\Phi_\Delta > 0.5$)[24] induce severe, widespread phototoxicity, reducing survival rates to 10−20%. The Fluorescein/ascorbate manifold generates $O_2^{\bullet-}$ and H_2O_2 continuously upon light activation, driving the bioorthogonal deboronative hydroxylation of a model *p*-boronated benzyl alcohol substrate to an 82% chemical yield within 30 min. By deliberately avoiding the indiscriminate $^1O_2$ pathway, we successfully established a biocompatible photocatalytic manifold that transitions seamlessly from test tubes to live cells, ensuring high cell viability during light-gated chemical bond cleavage.

2.2. First-Generation Systems: Cellular-Scale Modulation

These mechanistic principles were first implemented using exogenous organic dyes, defining the First Generation of Proximity-Activated Photocatalytic Pharmacology.[1] These early systems rely on the passive diffusion of low-molecular-weight organic dyes throughout the cellular matrix. Operating at micromolar concentrations (typically 10−100 μM), these freely diffusing dyes result in an unconstrained activation radius encompassing the entire volume of the cell.

Isopropyl-β-D-thiogalactoside (IPTG) was employed as a model inducer to validate the utility of visible-light photocatalytic deboronative hydroxylation within a living bacterial chassis (*E. coli* BL21(DE3)). In these experiments, the IPTG molecule was rendered biologically inert via premodification of its essential hydroxyl group into a caged boronate substrate (caged-IPTG, 200 μM). Under visible light irradiation, the triggered deboronative hydroxylation efficiently restored the inductive capability of the molecule by releasing active IPTG with its free hydroxyl group intact in high yield (75%). This liberated inducer successfully triggered downstream β-galactosidase expression (Figure 2B), confirming that our organic-dye photocatalytic system enables the controllable release of small-molecule effectors within a living system. This work demonstrated the feasibility of regulating photoinduced protein expression with spatiotemporal control, bridging the gap between synthetic photoredox catalysis and molecular biology.

These initial successes provided the critical mechanistic validation required to move toward more complex biological

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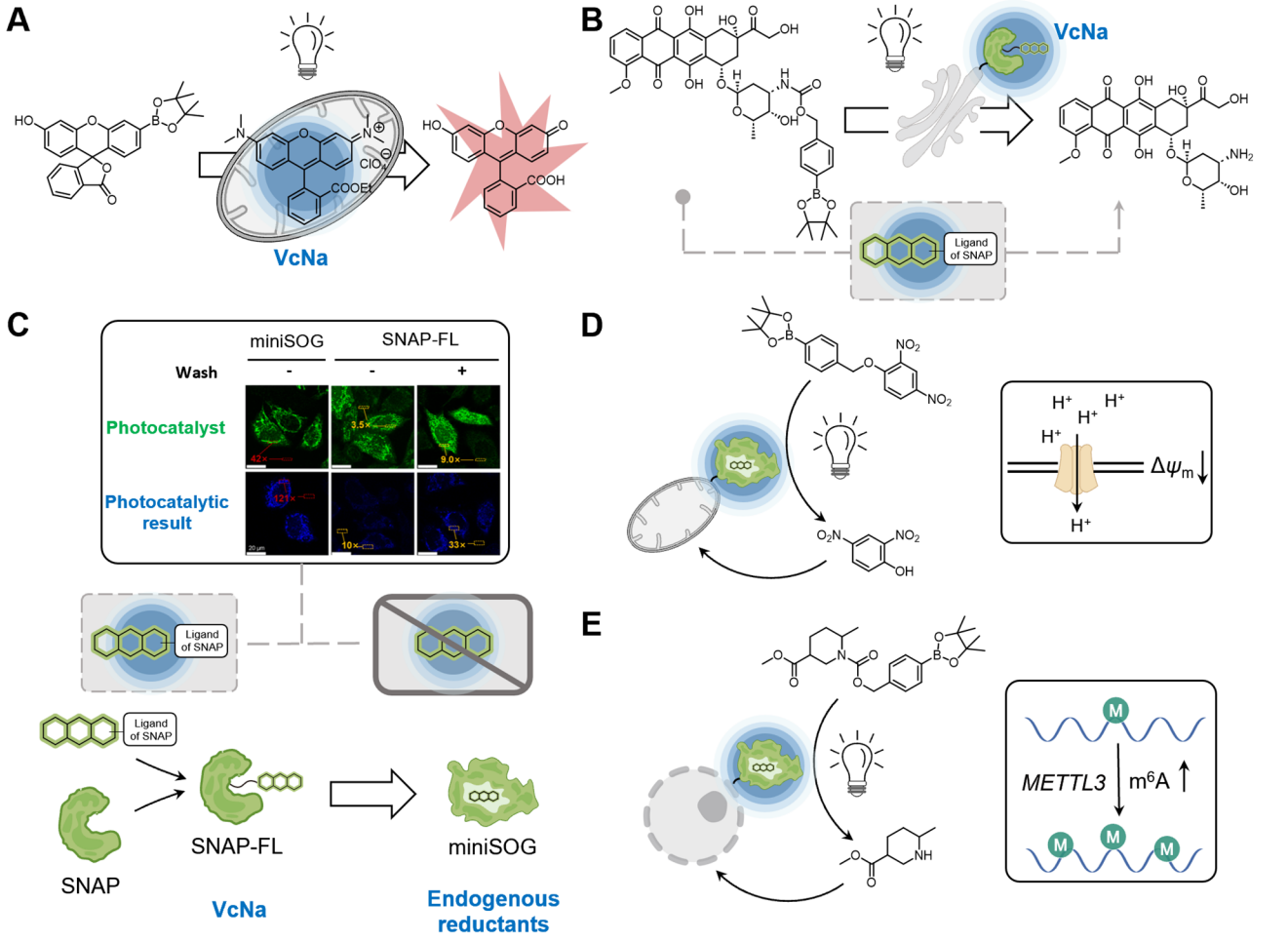

Figure 3. Subcellular Precision and Signal-to-Noise Optimization via Compartment-Targeted Photocatalysts. (A) Organelle-specific photocatalytic activation: Exploiting the mitochondrial localization of the cationic TMRE scaffold via electrochemical membrane potential to achieve location-restricted release of fluorogenic reporters within the mitochondria. (B) Comparative analysis and limitations of hybrid platforms: While organelle-targeted SNAP-FL fusions (across the nucleus, mitochondria, or ER) facilitate localized doxorubicin (DOX) release to deconvolute compartmentalized mechanisms like ER stress, these hybrid systems are susceptible to background interference arising from nonspecifically bound or residual small-molecule dye probes, necessitating a transition to autonomous photoenzymes for optimized fidelity. (C) Enhancement of Signal-to-Noise Ratio (SNR): The transition to the fully genetically encoded miniSOG eliminates the requirement for exogenous dye administration, yielding superior spatial fidelity and a significantly improved SNR by coupling chemical reactivity strictly to protein expression boundaries. (D) Selective mitochondrial depolarization: Mitochondria-targeted miniSOG (mito-miniSOG) achieves localized DNP release, enabling precise bioenergetic modulation and rapid dissipation of $\Delta\psi m$ within discrete subcellular microdomains without systemic uncoupling toxicity. (E) Precise modulation of the nuclear epitranscriptome: Nuclear-localized miniSOG (NLS-miniSOG) facilitates the targeted release of small-molecule epigenetic modulators, driving specific, linear increases in nuclear m^6A RNA methylation levels and downstream functional responses.

architectures. However, the reliance on exogenous administration and the lack of genetic targetability underscored the necessity of moving toward localized platforms. These early experiments constitute the definitive proof-of-concept stage of Photocatalytic Pharmacology (Figure 2C), establishing the conceptual foundation that would progressively refine the spatial boundaries of bioorthogonal photocatalytic reactions from the whole cell to discrete subcellular compartments and complex neural circuits.

3. ADVANCING SPATIAL FIDELITY: REACHING TRUE SUBCELLULAR PRECISION

While early first-generation systems provided foundational proof-of-concept evidence in cellular models, interrogating eukaryotic architecture required more precise spatial control. To transition from bulk cellular environments to discrete suborganellar coordinates, we sought to build boundaries directly within individual organelles. We achieved initial spatial restriction by exploiting the intrinsic physiochemical properties of specific organic dye scaffolds.[1] For instance, the delocalized lipophilic cation of a tetramethylrhodamine (TMRE) scaffold was utilized to drive electrophoretic mitochondrial targeting,[27] enabling the restricted release of fluorogenic reporters within mitochondria to establish our inaugural Proximity-Activated effect (Figure 3A).

3.1. From Passive Diffusion to Genetic Encoding

Building upon these early observations, subsequent investigations sought to generalize precise perturbation across diverse subcellular compartments. As the opening phase of our subcellular targeting campaign, we evaluated the biological consequences of compartment-specific drug release by employing the SNAP-tag system to tether synthetic fluorescein photocatalysts to distinct subcellular locales[28], including the

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plasma membrane, cytosol, nucleus, mitochondria, and endoplasmic reticulum (ER), within HeLa cells (Figure 3B).[2]

This approach enabled the organelle-confined photocatalytic liberation of doxorubicin (DOX), revealing markedly divergent cytotoxic outcomes based purely on spatial localization. Localized photocatalytic activation within the nucleus, mitochondria, or ER generated significant decreases in cell viability, whereas extra-organellar release at the plasma membrane or within the cytosol elicited no significant cytotoxic response. These findings not only corroborated classical mechanisms of DOX action via nuclear DNA intercalation and mitochondrial damage, but, crucially, revealed a previously unrecognized organelle-specific ER stress response induced by localized doxorubicin accumulation. This mechanistic insight had remained elusive to conventional methodologies due to their lack of spatial boundaries, highlighting the capacity of proximity-activated photocatalytic small-molecule release to deconvolute complex subcellular pharmacological mechanisms.

3.2. Optimization of the Signal-to-Noise Ratio (SNR)

A critical challenge in SNAP-FL system was the inherent background interference caused by nonspecifically bound or residual exogenous fluorescent dye probes.[29] While effective, these systems required stringent washing steps and remained susceptible to "chemical noise" from unbound dyes (Figure 3B).

The decisive advancement in our subcellular optimization campaign was the transition from hybrid architectures to fully genetically encoded miniature photoenzymes (miniSOG).[30] This platform design eliminates exogenous dye loading entirely and improves spatial fidelity by genetically restricting photocatalytic activity. Here, the reaction volume is no longer compromised by the diffusion or nonspecific occupancy of exogenous dyes, but is strictly governed by the intrinsic photochemistry of a monomeric 12 kDa protein scaffold utilizing endogenous cofactors. By adopting miniSOG, which utilizes an endogenous flavin mononucleotide (FMN) cofactor, we have eliminated the need for exogenous dye probe labeling altogether. This transition substantially improved both the signal-to-noise ratio (SNR) and spatial fidelity, ensuring that photocatalytic bond cleavage events are exclusively coupled to the genetic expression of the targeting protein. Furthermore, this autonomous configuration eliminates the requirement for exogenous reducing agents in live-cell applications (Figure 3C).[3]

3.3. Precise Perturbation of the Mitochondrial Microdomain

The compact size of miniSOG (12 kDa) allows for precise targeting of the photocatalyst to organelle-specific microdomains with minimal steric disturbance to the native environment. In our study of cellular bioenergetics, we expressed mitochondria-targeted miniSOG (mito-miniSOG) to catalyze the localized photouncaging of a boronate prodrug of 2,4-dinitrophenol (DNP) to release active DNP.

In HeLa cells, this localized photocatalytic release of DNP triggered rapid mitochondrial depolarization (>70% loss of $\Delta\psi m$) within only 5 min (Figure 3D). The accuracy of this Photocatalytic Pharmacology system is evidenced by its strict localization dependence: while mito-miniSOG induced near-complete depolarization (comparable to the canonical uncoupler FCCP), systemic release of DNP driven by cytosolic miniSOG failed to elicit any bioenergetic response. Furthermore, this approach maintained 94% cell viability, demonstrating that confining the reaction to the Proximity-Activated Zone (PAZ) prevents the severe off-target systemic toxicity typically associated with conventional mitochondrial uncouplers.[31]

3.4. Interrogating the Nuclear Epitranscriptome

The versatility of the PAZ extends beyond bioenergetics to the regulation of the nuclear epitranscriptome. The selective nature of the reaction sphere, governed by the submicrometer scale diffusion limit of $O_2^{\cdot-}$, enables the selective modulation of complex macromolecular signaling environments, such as the nucleus. We developed a nucleus-targeted variant (NLS-miniSOG) to facilitate the photocatalytic release of epigenetic modulators, specifically METTL3 agonists (Figure 3E).

This system achieved a 1.20-fold increase in m^6A hypermethylation exclusively within the nuclear compartment. The temporal control was exquisite, showing a linear accumulation of m^6A relative to visible light irradiation time ($R^2 = 0.99$). Notably, significant m^6A accumulation could be achieved with as little as 10 s of light exposure while maintaining negligible phototoxicity (>95% cell viability). Functionally, this localized epigenetic remodeling was sufficient to upregulate autophagy, evidenced by a 1.28-fold accumulation of the autophagic marker LC3-II.

By leveraging the confined photocatalytic reactivity of miniSOG, we have established a robust platform for manipulating energy metabolism and the nuclear epitranscriptome with minimal off-target effects. This evolution of subcellular deployment demonstrates that the physical composition and genetic localization of the photocatalyst serve as the critical determinants of biological outcomes, less dependent on substrate structure, solidifying the role of Photocatalytic Pharmacology as an indispensable tool for precision biology.

4. MOVING TOWARD COMPLEXITY: GENETIC TARGETABILITY AND CIRCUIT PRECISION FOR NEUROSCIENCE

Having established that proximity-activated platforms could resolve distinct pharmacological pathways within individual organelle microdomains, we sought to test this spatial fidelity in the ultimate organizational matrix: the mammalian nervous system. The mammalian nervous system comprises billions of neurons organized into highly specialized circuits that govern sensation, cognition, and behavior. Dysfunction within specific neural pathways underlies numerous neurological and psychiatric disorders, ranging from chronic pain to anxiety and addiction. Understanding how discrete cell types and their long-range projections contribute to circuit function, and how they can be targeted for precise therapeutic intervention, represents one of the most pressing challenges in modern neuroscience.[32]

The transition from bulk cellular modulation to the selective interrogation of complex neural circuits represents the defining milestone of the Third Generation of our platform: Circuit-Level Photopharmacology. Because neurons possess intricate, highly polarized architectures and exhibit exquisite sensitivity to local chemical gradients, they demand a degree of spatiotemporal precision that traditional pharmacology cannot provide.[33] This section charts the technological evolution of our platform as it transitions from initial *ex vivo* proof-of-concept validation in acute neural tissue toward the deployment of highly refined hybrid architectures capable of dissecting neural hierarchies in live, behaving animals with precise cell-type and projection specificity.

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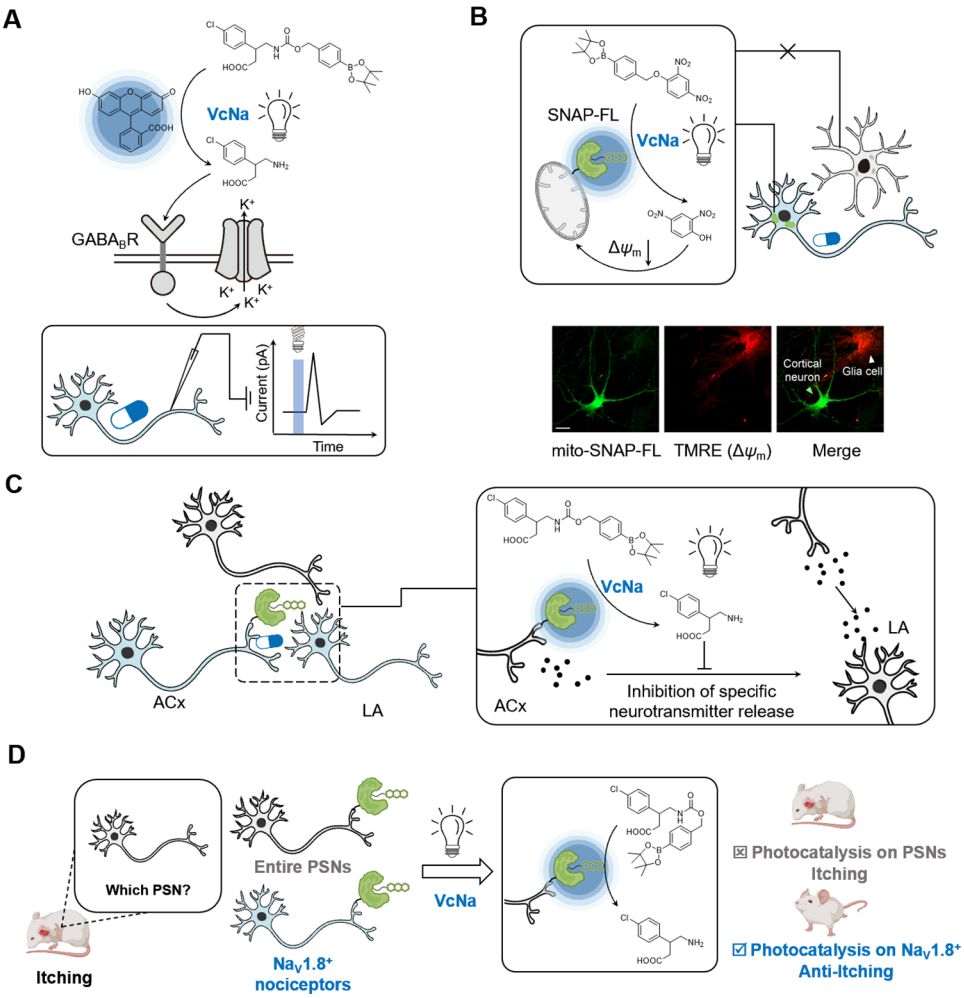

Figure 4. Cell-Type and Pathway-Specific Neuromodulation via Circuit-Targeted Photocatalysis. (A) *Ex vivo* neuromodulation in acute brain slices: Photocatalytic uncaging of a chemically caged baclofen derivative facilitates precise, light-gated control over neuronal membrane currents through the spatially confined activation of postsynaptic $GABA_B$ receptors. (B) Genetically targeted mitochondrial perturbation: Spatiotemporal control is achieved through the targeted expression of an outer-mitochondrial-membrane-anchored SNAP-tag; visible-light irradiation induces a significant, localized dissipation of $\Delta\psi m$ exclusively in genetically targeted cortical neurons via the proximity-activated liberation of DNP, while adjacent glial cells and untargeted cellular elements lacking the genetic construct remain unaffected. (C) Projection-specific interrogation of long-range circuitry: Utilizing the hybrid SNAP-FL platform to achieve pathway-specific presynaptic inhibition via localized baclofen release. Functional suppression of synaptic transmission and corresponding alterations in paired-pulse ratios (PPR) are strictly restricted to SNAP-tag-expressing auditory cortex (ACx) projections innervating the lateral amygdala (LA), demonstrating precise circuit control without bystander effects in neighboring, nonexpressing inputs. (D) *In vivo* discovery delineating the peripheral circuitry of itch: Leveraging cell-type-specific neuromodulation in freely behaving mice to map somatosensory pathways. While nontargeted, pan-sensory uncaging of baclofen fails to produce a therapeutic response due to competing sensory pathways, restricted release specifically at $Na_V1.8^+$ nociceptor somatic and axonal terminals effectively suppresses scratching behavior induced by acute pruritogen challenge.

4.1. Establishing Neuronal Compatibility and Temporal Control

Our foundational neuro-focused work established the first visible-light photocatalytic uncaging system compatible with the delicate, highly sensitive live neuronal microenvironment.[1] Utilizing a chemically caged baclofen derivative, a small-molecule agonist of the γ-aminobutyric acid type B ($GABA_B$) receptor,[34] we demonstrated that the localized photocatalytic generation of $O_2^{\cdot-}$ and H_2O_2 could trigger chemoselective deboronative hydroxylation to release active baclofen without compromising neuronal viability.

Whole-cell patch-clamp recordings in acute mouse brain slices revealed robust, light-triggered outward inhibitory currents (~12 pA) within minutes of visible-light irradiation due to the photocatalytic liberation of active baclofen; these outward currents were abolished by the selective $GABA_B$ receptor antagonist CGP52432. This study provided the vital proof-of-principle that Proximity-Activated Photocatalytic Pharmacology could achieve the requisite temporal control over neuronal excitability while maintaining the strict receptor specificity demanded by neuroscience (Figure 4A).

4.2. Subcellular Resolution: Genetically Targeted Mitochondrial Perturbation

To move beyond non-targeted bulk administration, we implemented a genetically targeted approach to direct synthetic organic dyes to precise subcellular coordinates within cultured neurons.[35] By fusing a SNAP-tag to mitochondria-targeting sequences, we achieved organelle-specific control via localized photocatalytic release within individual primary cortical neurons (Figure 4B).[2]

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Table 1. Comparative Profile of the Three Spatiotemporal Generations of Proximity-Activated Photocatalytic Platforms

generation	platform architecture	localization strategy	spatial scale	SNR	current frontiers and limitations
1st Gen	passive diffusion photopharmacology	passive diffusion and electrostatic membrane interactions of exogenous organic dye	whole-cell/limited organelle	good	limited spatial resolution and off-target background activation
2nd Gen	subcellular photopharmacology	exogenous dye loading onto SNAP-tags	general organelle coordinates	high (10×)	requires precise washing protocols and transfection optimization
		autonomous miniSOG expression		highest SNR in cell culture (121×)	requires transfection optimization
3rd Gen	circuit-level photopharmacology	genetically programmed expression in tissue slices and projection-specific terminals	neural networks/*in vivo* animal circuits	high	requires specialized viral delivery optimization (*in vivo*)

Upon treatment with the cell-permeable, diacetylated fluorescein-linked derivative (CLPDF) as the prephotocatalyst, the scaffold undergoes rapid intracellular esterase-mediated deprotection and becomes covalently anchored directly onto the genetically encoded SNAP-tag localized at the neuronal mitochondrial membrane. This precise subcellular localization enables the proximity-activated liberation of 2,4-dinitrophenol (DNP), driving a significant, localized dissipation of the mitochondrial membrane potential ($\Delta\psi m$).

Critically, this biophysical perturbation is strictly restricted to SNAP-tag-expressing neurons; adjacent glial cells and untargeted cellular elements lacking the genetic construct remain unaffected. This near-complete minimization of off-target bystander effects confirms that the photocatalytically released DNP is successfully confined within the targeted subcellular microdomain, preventing lateral diffusion between neighboring cells. By preserving the physiological integrity of the surrounding neural tissue, this platform demonstrates the exceptional signal-to-noise ratio (SNR) of proximity-activated logic within highly integrated, heterogeneous brain environments.

4.3. Projection-Specific Interrogation of Long-Range Neural Circuits

The structural and architectural complexity of the mammalian brain necessitates molecular tools that can modulate specific synaptic projections rather than entire, heterogeneous neuronal populations. We addressed this challenge by targeting inhibitory $GABA_B$ receptors ($GABA_BRs$) within the corticoamygdalar projection, a principal pathway governing sensory processing and emotional gating. By leveraging an adeno-associated virus (AAV) approach to express membrane-anchored SNAP-FL specifically at the presynaptic terminals of auditory cortex (ACx) neurons innervating the lateral amygdala (LA), we achieved projection-specific synaptic inhibition via the localized photocatalytic liberation of the $GABA_BR$ agonist baclofen (Figure 4C).[2]

Whole-cell electrophysiological assessments revealed that light-triggered presynaptic baclofen release produced robust increases in paired-pulse ratios (PPR) and corresponding decreases in evoked excitatory postsynaptic currents (EPSC), confirming the selective reduction of presynaptic neurotransmitter release probability. Strikingly, a mere 5 ms optical pulse was sufficient to suppress synaptic transmission, demonstrating that this proximity-activated optochemical platform achieves temporal kinetics comparable to traditional optogenetics. By combining this system with red-shifted optogenetic stimulation (via ChrimsonR expressed in the same input pathway), we established an orthogonal dual-optical framework. This configuration allows for the simultaneous, high-fidelity optical stimulation and chemical inhibition of discrete, long-range neural circuits within a single, intact tissue architecture.

4.4. In Vivo Discovery: Delineating the Circuitry of Peripheral Itch

The maturation of these spatiotemporal tools culminated in the first successful instance of cell-type-specific photocatalytic pharmacological neuromodulation in freely behaving animals, shifting our research program's focus from methodological validation to *in vivo* biological discovery.[2] While inhibitory GABAergic signaling via $GABA_B$ receptors ($GABA_BRs$) was known to suppress pruritus, the specific subsets of peripheral sensory afferents responsible for mediating this antipruritic effect had long remained elusive due to the spatial limitations of conventional systemic pharmacology.[36]

To resolve this ambiguity, we utilized Cre-dependent adeno-associated virus (AAV) vectors to restrict the expression of membrane-anchored SNAP-FL exclusively to $Na_V1.8^+$ nociceptors in mice, allowing us to directly compare the physiological outcomes of cell-type-specific optochemical activation with nontargeted, bulk sensory modulation (Figure 4D). Strikingly, while the nonselective, bulk photocatalytic liberation of baclofen across the entire peripheral sensory neuron (PSN) population failed to produce a discernible behavioral or therapeutic response, the restricted release of baclofen specifically within $Na_V1.8^+$ using an identical concentration significantly decreased histamine-induced scratching behavior.

Furthermore, this highly localized activation robustly attenuated the upregulation of the immediate-early gene c-Fos in the superficial laminae of the spinal cord dorsal horn, providing definitive cellular evidence of suppressed central itch transmission. This discovery successfully identified $Na_V1.8^+$ nociceptors as the critical, necessary cellular gateways mediating $GABA_BR$-dependent antipruritic signaling. By successfully attenuating experimentally induced acute itch with high genetic specificity *in vivo*, this work underscores the unique power of Proximity-Activated Photocatalytic Pharmacology to dissect and resolve complex, interconnected cellular hierarchies that remain inaccessible to conventional small-molecule modalities.

5. THE MECHANISM OF PRECISION: EVOLUTIONARY TRAJECTORY AND THE SET PATHWAY

The maturation of Photocatalytic Pharmacology has been defined by a stepwise enhancement in our capacity to interrogate distinct biological boundaries (Table 1). Ultimately, the transition from unconstrained chemical dyes to hybrid fusions and miniature photoenzymes was driven not merely by a desire for structural variety, but by the necessity to meet the rigorous spatial demands of organelle architecture and complex neural wiring. As our laboratory transitioned from exogenous bulk components to fully genetically encoded photoenzymes, we

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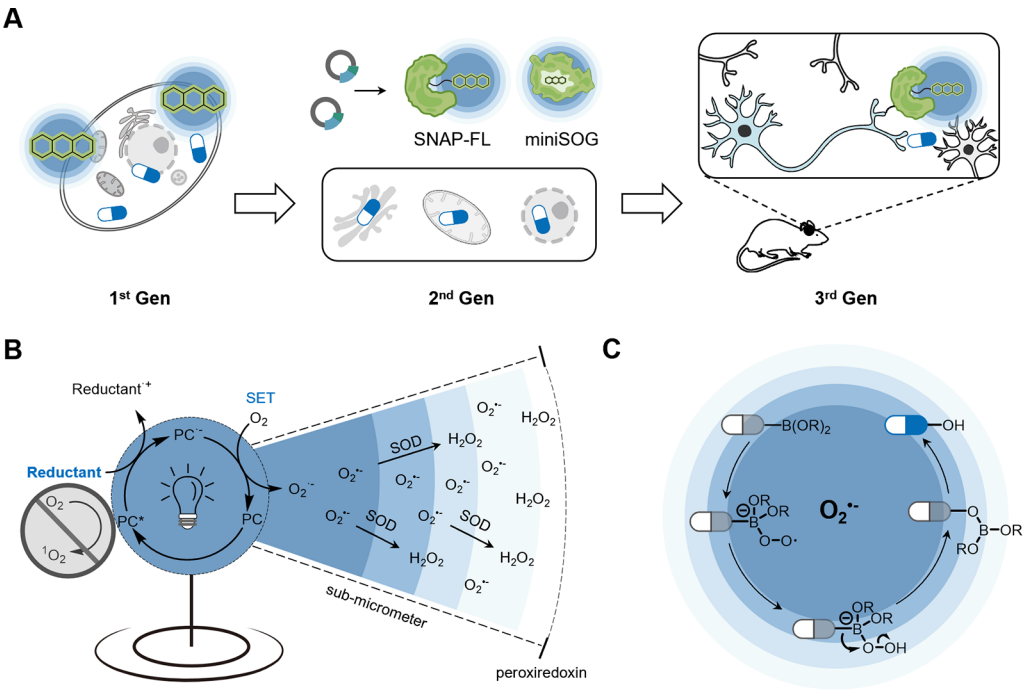

Figure 5. Mechanistic Principles and Spatial Logic of Proximity-Activated Photocatalytic Pharmacology. (A) Evolutionary trajectory of photocatalytic platforms: The structural and functional progression from unconstrained organic dyes to hybrid SNAP-tag architectures and fully genetically encoded miniature photoenzymes (miniSOG) has yielded a stepwise enhancement in subcellular localization precision, signal-to-noise ratio (SNR), and structural compatibility within complex living systems. (B) The Proximity-Activated Zone (PAZ) governed by reactive species diffusion: SET from the reduced photoexcited photocatalyst to molecular oxygen generates $O_2^{\cdot-}$. Within the crowded intracellular environment, the effective diffusion radius of these species is restricted to a submicrometer scale via endogenous enzyme-mediated quenching, creating a high-resolution reaction sphere centered strictly around the photocatalyst's physical coordinates. (C) Unified mechanism of superoxide-mediated deboronative hydroxylation: The transient $O_2^{\cdot-}$ species acts as the primary chemical effector, attacking the organoboron center for deboronative hydroxylation.

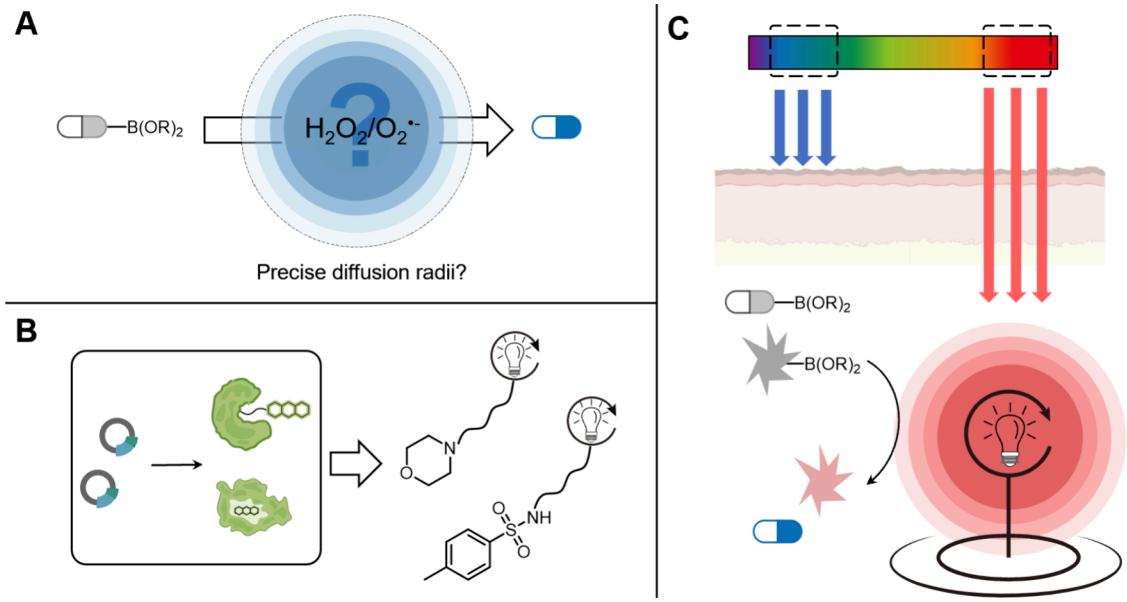

Figure 6. The Current Limitation and Future Landscape of Proximity-Activated Photocatalytic Pharmacology. (A) Decoupling intermediate dynamics: Investigating the competitive reaction kinetics and real-time diffusion behaviors of $O_2^{\cdot-}$ and H_2O_2 to precisely map the concentration gradients within the reaction sphere. (B) Nongenetic precision targeting: Designing alternative chemical strategies using synthetic Small Molecule–Photocatalyst Conjugates (SMPCs) to localize to specific cellular compartments, bypassing translational genetic barriers. (C) Deep-tissue optical interrogation: Developing red-shifted and near-infrared (NIR) activated photocatalytic systems to achieve noninvasive signaling modulation and targeted therapeutic interventions in whole-animal models.

integrated a photocatalytic SET pathway of molecular oxygen with the native chemical quenching machinery of the cell, thereby precisely delineating the spatial boundaries within which bioorthogonal transformations are permitted to occur (Figure 5A). These SET-generated species are biocompatible chemical intermediates that provide the high chemoselectivity

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necessary to trigger bioorthogonal prodrug activation via deboronative hydroxylation without disrupting cellular homeostatic balance.

The exceptional spatial fidelity of our platforms arises from the privileged, short-lived reactivity of these SET-generated species within a crowded, enzymatically active biological context. Within the intracellular environment, $O_2^{\cdot-}$ and H_2O_2 are rapidly sequestered and metabolized into benign, nonreactive species by endogenous superoxide dismutases (SODs), catalases, and related cellular antioxidants.[26] This enzymatic quenching acts as a natural spatial filter, restricting the effective diffusion of $O_2^{\cdot-}$ and H_2O_2 to a submicrometer reaction sphere centered precisely at the photocatalyst's physical coordinates (Figure 5B).

These transient $O_2^{\cdot-}$ and H_2O_2 species serve as the primary chemical effectors, triggering the deboronative hydroxylation of organoboronates via a unified cargo-release mechanism (Figure 5C). Whether the protected cargo is a fluorophore, an epigenetic agonist, or a neuromodulator like baclofen, the bond-cleavage event is precisely confined to the targeted Proximity-Activated Zone (PAZ). This conceptual framework successfully merges fundamental photoredox catalysis with high-resolution biology, providing a robust pathway for the precise interrogation of complex biological signaling hierarchies.

6. CURRENT LIMITATIONS AND OUTLOOK

Precise spatiotemporal control over molecular events remains a central challenge in chemical biology.[37] Despite the remarkable evolution of Proximity-Activated Photocatalytic Pharmacology, key limitations and mechanistic ambiguities persist that must be resolved to realize its full biological and therapeutic potential. From a mechanistic standpoint, a fundamental ambiguity remains regarding which specific intermediate dominates the deboronative hydroxylation cascades. While both $O_2^{\cdot-}$ and H_2O_2 are capable of reacting with organoboronates, the rapid dismutation of $O_2^{\cdot-}$ into H_2O_2 creates an interconnected chemical reactivity chain. The quantitative contribution of each distinct species to the final uncaging event has not yet been fully decoupled, and their precise intracellular diffusion radii under physiological conditions remain to be established through definitive kinetic experimentation (Figure 6A).

Another translational limitation of our current methodology is its heavy reliance on genetic encoding (such as SNAP-tag fusions or miniSOG scaffolds) to achieve subcellular localization. While powerful for laboratory interrogation, genetic delivery remains a significant translational barrier for clinical applications. The long-term expression effects, metabolic stability, and potential immunogenicity of these non-native protein scaffolds in live animals remain largely unexplored.

Furthermore, similar to other photochemical tools, our platform is strictly dependent on light irradiation. Therefore, light source selection remains a primary consideration in system design and optimization. For example, our current reliance on short-wavelength visible light (blue to green) restricts photon tissue penetration depth, thereby limiting current *in vivo* applications primarily to superficial tissues or optically accessible biological models, a constraint we are actively addressing through the development of red-shifted and NIR-activated systems.

Consequently, the next frontier of Photocatalytic Pharmacology will be defined by three major directions: (i) Decoupling Intermediate Dynamics: Further investigating the fundamental reaction kinetics and precise *in vivo* diffusion behaviors of $O_2^{\cdot-}$ versus H_2O_2 to map the exact dimensions of the Proximity-Activated Zone (PAZ) (Figure 6A); (ii) Non-Genetic Targeting Strategies: Developing alternative, translationally viable localization strategies, such as engineering synthetic Small Molecule−Photocatalyst Conjugates (SMPCs) that exploit endogenous cellular receptors or organelle-homing ligands, including morpholine motifs for lysosomal sequestration or *p*-toluenesulfonamide moieties for endoplasmic reticulum localization, to achieve high-resolution compartment targeting without genetic modification (Figure 6B);[38] (iii) Near-Infrared (NIR) Activation: Expanding proximity-release strategies toward red and near-infrared (NIR) wavelengths systematically overcomes the intrinsic limitations of conventional UV−visible systems, including restricted tissue penetration, elevated phototoxicity, and background interference (Figure 6C). Shifted activation thresholds thereby enable noninvasive, deep-tissue delivery and precise therapeutic intervention in complex, whole-animal models.[39]

By bridging fundamental synthetic photochemistry with the intricacies of cellular architecture, proximity-activated photocatalytic deboronative hydroxylation has evolved from a synthetic methodology into a robust bioorthogonal technology, establishing a rigorous foundation for the future of Photocatalytic Pharmacology.

7. CONCLUSION

The evolution from exogenous organic dyes to hybrid, genetically targeted platforms and autonomous miniature photoenzymes represents a major advancement in the development of Photocatalytic Pharmacology, transitioning the field from an *in vitro* synthetic methodology into a high-precision modality for biological interrogation. By shifting the design priority from substrate scope optimization to the precise physical coordinates of the catalyst, we have established a robust framework where the Proximity-Activated Zone (PAZ), a submicrometer reaction volume strictly governed by short-lived intermediates and endogenous cellular quenching, dictates the pharmacological outcome.

Our research demonstrates that transient, highly reactive chemical species can be safely harnessed for selective biological modulation when their free diffusion is restricted through rational catalyst engineering and the strategic exploitation of native metabolic sinks. The expanding application of these tools across chemical biology and neuroscience is driving the development of next-generation photocatalytic systems that are genetically modular, highly biocompatible, and active within dense, complex biological architectures under physiological aerobic conditions.

As we continue to refine the spatiotemporal logic of this field, Proximity-Activated Photocatalytic Pharmacology offers an essential paradigm for the precise interrogation and modulation of dynamic, interconnected signaling networks. By bridging synthetic photoredox chemistry with cellular architecture, this approach provides a versatile toolkit capable of decoding biological hierarchies across multiple spatiotemporal scales, from subcellular organelle microdomains to long-range neural circuits. Ultimately, this conceptual transition from bulk reaction engineering to spatial compartmentalization establishes Photocatalytic Pharmacology as a foundational pillar for the future of optically controlled pharmacological intervention.

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