A Self-Assembled Nano-PROTAC Enables Near-Infrared Photo-dynamic Proteolysis for Cancer Therapy

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Confining the protein degradation activity of proteolysis-targeting chimera (PROTAC) to cancer lesions ensures precision treatment. However, it still remains challenging to precisely control PROTAC function in tumor regions in vivo. We herein describe a near-infrared (NIR) photo-activatable nano-PROTAC (NAP) for remote controllable proteolysis in tumor-bearing mice. NAP self-assembles from an amphiphilic conjugate of PROTAC linked with an NIR photosensitizer through a singlet oxygen ($^1O_2$)-cleavable linker. The activity of PROTAC is initially silenced but can be remotely switched on upon NIR photoirradiation to generate $^1O_2$ by the photosensitizer. We demonstrated that NAP enabled tumor-specific degradation of bromodomain-containing protein 4 (BRD4) in a NIR light-instructed manner. This in combination with photodynamic therapy (PDT) elicited an effective suppression of tumor growth. This work thus presents a novel approach for spatiotemporal control over targeted protein degradation by PROTAC.

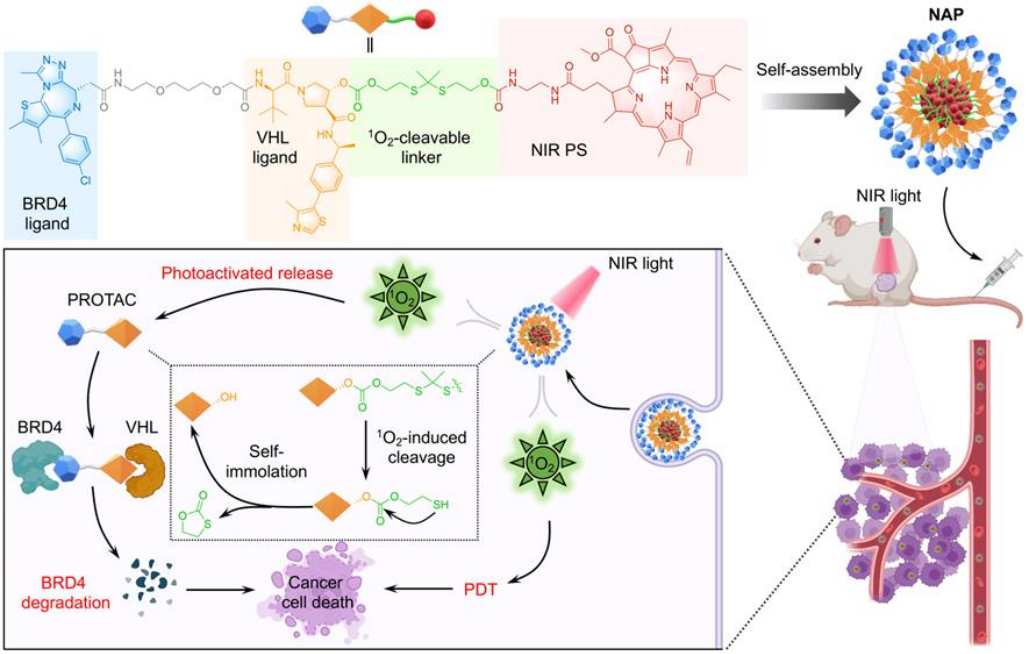

Figure 1. Schematic illustration of synthesis and NIR photoactivation mechanism of NAP for spatiotemporal control over PROTAC and synergistic cancer treatment.

References

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