Killing cancer cells is easy. We have lots of ways to do it. For example, something as simple as a jar of formaldehyde stops respiring tissues in their tracks. Killing cancer cells while leaving the surrounding tissue intact is much harder. Despite decades of research, cancer treatment remains a therapeutic regime that often combats cancer at the expense of patient health. Because current cancer chemotherapies can be potent even in minute concentrations, these cytotoxic compounds wreak havoc on neighboring healthy cells en route to their intended target. Thus, the problem often becomes one of delivery and specificity.

In this issue of ACS Central Science, Nani and co-workers introduce what may be an improved solution to the problem of delivering the highly toxic chemicals necessary to slay cancer cells, while avoiding deleterious effects to bystander tissues. To accomplish this feat, the authors combine two concepts for cancer therapy: antibody–drug conjugates (ADC) and photodynamic therapy (PDT) to generate a molecular triple threat (Figure 1). Their result: a cancer-targeting antibody, a potent cellular toxin, and controlled release using a new, light-responsive linker. The idea to conjugate drug molecules to antibodies is not a new one. In fact just in the past few years, two separate ADCs have been clinically approved for use in the United States, with more in clinical trials and in drug company pipelines. Yet, challenges to the widespread deployment of ADCs remain. Due in part to their size, delivery of the drug cargo to intracellular targets can be problematic. In addition, cancer-targeting antibodies must first attach themselves to their respective cell-surface antigen, meaning that an ADC approach’s success also critically depends on the high overexpression of cancer-specific markers on cancer vs normal cells.

Analogously, the use of light to generate cell-toxic species is also not new. Photodynamic therapy (PDT) uses a chemical agent that can absorb light energy and can convert relatively benign oxygen molecules into their more destructive cousins, reactive oxygen species (ROS). If the ROS are generated in close proximity to a tumor, one hopes the tumor bears the brunt of the injury relative to healthy tissue. But much like traditional chemotherapeutics, without targeting, ROS often don’t distinguish between healthy and diseased tissues, attacking both equally.

Miller discusses how clever molecular design can create a cancer triple threat.

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In this study, Nani and co-workers reevaluate their original ADC configuration, with special attention to the relationship between the stability of the cyanine linker in the dark and the rate of light-induced drug release. What is unique about the work of Nani and co-workers is that they combine the best of all of these strategies using carefully considered chemistry. Linking a potent cytotoxin to a cancer-targeting antibody through a light-sensitive linker, they create something uniquely effective and, one hopes, much more innocuous to healthy tissue. The linkage between drug and antibody masks the functionality that is important for the drug’s mode of action, creating a “prodrug” which is released and activated only in the presence of light. The critical component here is the light-sensitive linker developed in the Schnermann lab. Schnermann and his group have been pioneering the use of cyanine dyes as photoreactive “caging” groups that can be installed on a molecule of interest to mask its native function. Then, at the appropriate moment, the native function of the molecule can be restored upon illumination with light. So-called photocaging has found wide application in a number of fields, ranging from photolithography to systems neuroscience, but the majority of photolabile compounds use high-energy light, in the UV or near-UV range. This is less than ideal for applications where the light must traverse a thick, opaque tissue to reach its intended target. To surmount this challenge, Schnermann and colleagues exploit the unique photochemistry of polymethine dyes which, in certain configurations, can be induced to undergo a photochemical rearrangement, followed by hydrolysis. The photochemical reaction results in a loss of fluorescence and the hydrolysis reaction fragments the cyanine dye, releasing any cargo which had been chemically appended to the dye. These properties allowed Schnermann and his group to link duocarmycin—a potent DNA alkylating agent—to panitumumab, a monoclonal antibody against the epidermal growth factor receptor (EGFR), in a configuration that places the cyanine dye between drug and antibody to act as a light-triggered release valve. The use of cyanine-based light-reactive linkages between the antibody and caged drug, instead of more traditional release cues like protons, thiols, or proteases, enables more precise delivery of therapies.

In this study, Nani and co-workers reevaluate their original ADC configuration, with special attention to the relationship between the stability of the cyanine linker in the dark and the rate of light-induced drug release. They predict that the simple substitution from methyl to ethyl at the cyanine bridgehead would both improve hydrolytic stability—on account of the more bulky substituent blocking nucleophilic attack by water—and induce a spectral shift toward longer wavelengths. Both properties, improved stability in the absence of light and longer wavelengths, are beneficial when using light-triggered chemotherapy release in living animals. In a series of careful in vitro studies they found that, indeed, the ethyl substitution gave the predicted bathochromic shift, maintained photooxidation and drug release kinetics, and improved hydrolytic stability. They then synthesized both methyl and ethyl flavors of duocarmycin–cyanine–panitumumab conjugates and tested their abilities to kill cancer cells in the presence and absence of light. In tissue culture models, the ethyl cyanine ADC showed an 8-fold improvement in the light/dark therapeutic index compared to their first-generation ADC. Control experiments with cells that do not express EGFR showed little therapeutic benefit, demonstrating the specificity of the authors’ design. The light sensitive ADCs performed equally well in mouse models of EGFR(+) cancer. In single drug administration + light administration, mice treated with the drug showed decreased tumor volume and improved life expectancy when compared to the vehicle-treated mice or mice who received the ADC, but no light.

In summary, this study represents a powerful method to combine PDT and ADC to deliver chemotherapies to tumors. The study also highlights the power of moving from molecules to mice, as a comprehensive understanding of the mechanisms behind the photocaging reactivity allowed the redesign and synthesis of more effective light-sensitive linkers. “Plug and play” strategies, where potent chemotherapy can be mixed and matched with arrays of monoclonal antibodies, may be enabled by this particular approach and would represent an important advance in cancer treatment. The improvement in hydrolytic stability, while enabling in this case, was fairly modest, at approximately 2-fold. Will more bulky substituents like isopropyl or tert-butyl improve dark stability? Is it possible to separate the dark hydrolysis from the light-enabled hydrolytic reaction? Finally, for in vivo applications, the pharmacokinetics and metabolic stability of the cyanines need to be more fully explored, as should alternative drug and light dosing schemes.
Killing cancer cells selectively remains a difficult task, but the careful application of synthetic chemistry and photochemistry is teaching us new ways to think about how to target and treat cancer.

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