Shooting Cancer With Magic Bullets*
Promises and Challenges of Antibody-drug Conjugates

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Antibody-drug conjugates (ADCs) are strategically designed formulations for the targeted elimination of cancer cells without causing severe side effects. ADCs first recognise and bind to specific receptors on cancer cells and then enter the cells via endocytosis. Inside the cells, the cytotoxic agent attached to the ADC is released and kills the cells by disrupting the latter’s defined target. Despite their superior efficacy over classic chemotherapeutics, ADCs face drug resistance in some patients. Novel ADCs are in development to address these challenges.

Cancer therapeutic research can be viewed as an ever-escalating battle between human intelligence and the so-called intelligence of cancer cells. Effective treatment aimed at the complete cure of advanced tumours is very challenging. The reason is simple! Cancer cells are not foreign pathogens that invade the human body. Rather, they are one’s own cells that refuse to obey the chains of commands required for peaceful coexistence with their neighbours. Not only do they become cancerous, they sometimes migrate to distant parts of the body and begin colonising—a process called metastasis. This is not to assume, however, that cancer cells have an easy way forward. Firstly, to become cancerous, the cells need to acquire multiple, successive mutations in their DNA. At every stage of their transformation, these cells are challenged by our body’s immune defence system. If the cells refuse to end their existence via internally executed programmed cell death, then cells of the immune system will attempt to destroy them via diverse mechanisms, including antibody-dependent cell-mediated cytotoxicity. Even the migration of cancer cells from

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Figure 1. The mechanism of action of the antibody-drug conjugate, Kadcyla. A tumour-targeted antibody (trastuzumab) attached to a cytotoxic agent (DM1) recognizes a receptor (HER2) present predominantly on HER2 + breast cancer cells and bind to it. After the binding, the ADC is internalized via endocytosis. Once inside, DM1 molecules are released via lysosomal degradation of the ADC, and they then attack their target (microtubules), prompting cell death (see [2]). (Credit: The figure was created using Biorender software.)

However, some cancer cells survive all these challenges, multiply aggressively, migrate and colonise different parts of the body. How, then, to selectively eliminate these cells? One strategy to eliminate cancer cells without harming normal tissues is to find certain proteins that are displayed specifically or predominantly on the surface of the cancer cells. Once identified, an antibody-drug conjugate (ADC) can be designed [2–4]. Like most other anticancer drugs in the market, the development of ADCs also takes several years of painstaking efforts and a lot of money. Without a doubt, these novel therapeutics fare much better than several conventional cancer therapeutics. Also called the ‘magic bullets’ for cancer therapy, ADCs have improved the outcome of treatment by prolonging the lifespan of patients and reducing many side effects. An ADC consists of a cytotoxic drug molecule that has a defined cellular target (e.g., DNA, microtubules), a linker that is engineered to remain stable in the circulation after injection and cleaved once the ADC enters the cancer cells, and an antibody

1 The term ‘magic bullet’ was coined by the German scientist Paul Ehrlich to describe drugs that can bring forth desired effects without inducing dangerous side effects.
that can recognise antigens (e.g., certain growth factor receptors) that are present specifically or predominantly on the cancer cells [2]. Once the ADC reaches the target tumour cells, it gets inside the cells via a process termed ‘receptor-mediated endocytosis’. Once inside, the linker is cleaved, and the liberated drug kills the cells it gained entry to. Kadcyla is one such ADC used for the treatment of a type of breast cancer called HER2+ breast cancer. These cancer cells show excessive expression of a growth factor receptor protein called human epidermal growth factor receptor-2 (HER2). The antibody component of Kadcyla, trastuzumab, binds to HER2. Subsequently, the ADC enters inside the cells via endocytosis. Once inside, lysosomal degradation liberates the ADC’s cytotoxic agent, ado-trastuzumab emtansine (DM1). DM1 then attacks its target, the microtubules (Figure 1). Specifically, DM1 molecules inhibit the normal assembly dynamics of microtubules, leading to the death of the cells [3–4]. Interestingly, ADC-treatment can eliminate not only the cells in which they have entered but also the neighbouring cancer cells. This happens when the drug-afflicted cell dies, and the drug molecules subsequently released attack the cells in their immediate vicinity. This passive yet very facilitatory effect is called the ‘bystander killing effect’. ADCs fare considerably better than many conventional chemotherapeutic strategies and bring forth promising outcomes.

In some patients, however, a few of the cancer cells subjected to bear the brunt of this treatment strategy learn to mount resistance against it. Cancer cells employ two major tricks to thwart ADCs. The first one is to remove the portion of the cell-surface protein that binds the antibody. The ADC then becomes helpless as it has nothing to bind to. The second trick is to grow some ‘shields’ over the antibody-binding sites of the proteins. Cancer cells usually utilise mucin² and hyaluronan³ to mask the sites. Nevertheless, despite these challenges, ADC has been emerging as a highly efficacious treatment strategy for many cancers. Efforts are in full swing to optimise the design of ADCs to enhance the elimination of cancerous cells with negligible off-target tox-

² A heavily glycosylated protein.
³ A polysaccharide.
icity. Some well-known ADCs that are currently in clinical use include—Mylotarg (gemtuzumab ozogamicin) for acute myeloid leukaemia, Adcetris (brentuximab vedotin) for Hodgkin lymphoma, Kadcyla (ado-trastuzumab emtansine) for HER2-positive breast cancer, Besponsa (inotuzumab ozogamicin) for some forms of acute lymphoblastic leukaemia, and Polivy (polatuzumab vedotin-piq) for some forms of B-cell lymphoma [5].

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