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A Short Note on Monoclonal Antibodies in Cancer Drug Discovery

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DESCRIPTION

With increasing life expectancy, the number of cancer cases has reached unprecedented levels. In this scenario, the pharmaceutical industry is investing heavily in this therapeutic area. Despite these efforts, cancer drug discovery remains a very challenging field and therapeutic innovations have yet to yield the expected clinical results. However, the physiopathology of this disease is now better understood and the discovery of new molecular targets has renewed hopes for the development of improved therapies. Several notable advances have been made, the most important of which is the development of targeted therapies. Monoclonal antibodies and antibody-small molecule conjugates have emerged as promising approaches to improve drug selectivity and reduce side effects, posing the greatest challenges in oncology drug discovery. When the nitrogen mustard alkylated mechlorethamine was his first cancer drug to hit the market, the world's life expectancy was his 46.8 years. However, this demographic change is increasing the number of deaths associated with age-related diseases such as cancer. This makes cancer the second leading cause of death in the world today. Therefore, despite the large number of anticancer agents currently on the market, the constant development of new antitumor agents remains one of the most important public health needs.

Compounds that act as antimetabolites, DNA alkylating agents, microtubule disrupting agents, and compounds that inhibit DNA synthesis are classified as cytotoxic agents. These molecules act as less selective toxicants and, despite their potency, offer a narrow therapeutic window. This class includes ground-breaking antineoplastic agents developed in the late 1940s. Another class of oncology drugs, called targeted therapies, consists of molecules that modulate the activity of proteins specifically involved in tumorigenesis and cancer progression. Examples of these drugs are mAbs and small molecules that interfere with specific signaling pathways associated with malignant transformation. In general, mAbs do not permeate cell membranes and instead act on proteins on the cell surface. Alternatively, small molecules enter cells and disrupt signaling pathways by acting on intracellular molecular targets. A notable small-molecule targeted therapy is imatinib, a selective inhibitor of the BRC-Abl tyrosine kinase overexpressed in Chronic Myelogenous Leukemia (CML). Imatinib is a pioneering targeted therapy and breakthrough in cancer drug discovery. Imatinib has had tremendous clinical success, being approved and widely prescribed for more than 8 types of cancer.

Using antibodies as a system to selectively deliver cytotoxic drugs to tumor cells is another approach to explore synergy between targeting and cytotoxic compounds. ADC therapy aims to reduce side effects associated with the non-selective nature of cytotoxic drugs. The conjugate is designed to remain non-toxic until it reaches the targeted neoplastic tissue. This system allows selective delivery of drugs to cancer cells after linker cleavage. Therefore, to develop an effective ADC, these three components must be optimized. FDA-approved ADCs are currently available and they are brentuximab vedotin and adtrastuzumab emtansine. Current pharmaceutical research has brought to market innovative medicines that exert their pharmacological effects through unprecedented mechanisms of action. Despite the advances made in the field of advanced targeting exemplified by the development of venetoclax, most of these proteins are still poorly understood.

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CONFLICT OF INTEREST

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