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Precision medicine using monoclonal antibodies in cancer therapy

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EDITORIAL

Cancer is among the most threatening diseases in the world resulting in 19.3 million new cases and causing 10 million deaths in 2020. Female breast cancer is the most diagnosed with 2.3 million new cases (11.7% of total new cancer cases), followed by lung (11.4%), colorectal (10%), prostate (7.3%) and stomach (5.6%). It was recorded that lung cancer is still the leading cause of cancer death with 1.8 million deaths (18% of total cancer deaths) followed by colorectal (9.4%), liver (8.3%), stomach (7.7%) and female breast (6.9%) (Sung et al., 2021).

Presently, the use of monoclonal antibodies (mAbs) or immunotherapy is considered one of the main components in cancer therapy together with chemotherapy, surgery and radiation. The monoclonal antibody is a biological macromolecule that is known as a therapeutic protein. The protein-based molecules have led the top selling drugs for a few consecutive years. At the end of 2023, the global total drug revenue was led by immunology ($35.23 billion in revenue), oncology ($64.41 billion), and infectious diseases ($39.95 billion) (Bunts, 2023). Keytruda® overtook the position of Cominarty® Covid-19 vaccines over the declaration of the lifting of Covid-19 on 5 May 2023 by the World Health Organization. Keytruda® uses pembrolizumab as the monoclonal antibody to treat melanoma, lung cancer, cervical cancer, head and neck cancer, stomach cancer, and breast cancer.

Antibodies are secreted by B lymphocyte cells in response to the introduction of foreign antigens. A monoclonal antibody is a Y-shaped immunoglobulin which possesses two antigen-binding fragments (Fb) and a crystallisable fragment (Fc). They specifically bind to specific antigens molecules and inactivate the invader by blocking signalling pathways or inducing cell death (Ebrahimi & Samanta, 2023). Therapeutic monoclonal antibodies are the immunoglobulins that have been engineered to recognise certain antigen targets.

The practical and feasible production of monoclonal antibodies via hybridoma technology was first described by Kohler and Milstein in 1975 by fusion of mouse myeloma and isolated mouse spleen cells after the introduction of antigen into the mouse donor (Köhler & Milstein, 1975). Since then, potential therapeutic applications of monoclonal antibodies have been apparent. Following active research and development, OKT3 was the first monoclonal antibody developed in a clinical trial in 1986. However, it has safety and efficacy concerns due to immunogenic reactions. As a strategy, recombinant DNA technology has been introduced to modify the structure of monoclonal antibodies to chimeric and humanised monoclonal antibodies. Later, a fully human monoclonal antibody was designed using a variety of technologies ranging from original (natural) or synthetic libraries of human antibodies (Guimaraes Koch et al., 2022).

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Pembrolizumab is an immunoglobulin G4κ (IgG4-kappa) isotype antibody, an FDA-approved monoclonal antibody that works against programmed cell death protein 1 (PDP-1) on T-cell lymphocytes. It was initially used to treat advanced melanoma in 2014. Subsequently, it has been approved for many types of cancers. Pembrolizumab itself is a humanised antibody. It can be recognised from its infix name "zu" is humanized. The suffix "mab" refers to monoclonal antibodies according to the International Nonproprietary Names (INN) Programme of the World Health Organisation. However, since 2021 INN discontinued using the suffix mab due to the abundance number of products with mab in the market. It will be replaced with *-tug*, *-bart*, *-mig*, and *-ment* (Guimaraes Koch et al., 2022).

The specific targeting of monoclonal antibodies against antigens that are uniquely overexpressed by tumour cells has opened the opportunity to develop many other antibodies against specific cancers. The general mechanism of antibodies is inducing cell death by blockade of growth factor receptor signalling (Zahavi & Weiner, 2020). Overexpression of epidermal growth factor receptor (EGFR) by many different cancers led to the discovery of cetuximab which is anti-EGFR and able to induce apoptosis in tumour cells. Ovarian and breast cancers overexpress human epidermal growth factor receptor 2 (HER2) and tyrosine kinase receptor has inspired the development of trastuzumab. Anti-CD20 monoclonal antibody, ofatumumab is postulated to destroy B cells via several pathways including complement-dependent cytotoxicity (CDC) which is used to treat multiple sclerosis along with rituximab (Hauser et al., 2023).

In conclusion, the success story of antibody-drug conjugation (ADC) has been achieved by brentuximab vedotin (Adcetris®), and trastuzumab emtansine (Kadcyla®) for the treatment of Hodgkin lymphoma and breast cancer, respectively. The magic bullet theory of Paul Erlich (1854-1915) on the use of monoclonal antibodies has been able to identify the target without any side effects on the body. It has a great opportunity to be used in delivering cytotoxic drugs to the tumour site and benefiting a synergistic effect of the monoclonal antibody action. This concept will be an interesting point regarding the use of mAbs in cancer therapy.

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