Monoclonal antibodies: a new era in the treatment and prevention of disease

Background

Antibodies are one of the primary ways the body defends itself against disease. They work by binding specifically to their targets (viruses, virus-infected cells, epitopes expressed on cancer cells, etc.) and either interfering with their pathogenic effects or flagging them for clearance or destruction. Most, if not all, licensed vaccines also work by inducing antibodies against a specific pathogen.

Antibodies are also one of the most powerful tools in modern medicine. Single antibodies or monoclonal antibodies (mAbs) can bind specifically to their targets. They can also be engineered to optimise their binding, functional activity or half-life. They are typically more effective and less toxic than other less-specific therapies and can be used to either directly or indirectly boost the immune system’s ability to fight disease (such as cancers). In the case of autoimmune disease treatment, monoclonal antibodies can specifically block key pathologic processes or downstream effects of aberrant host immune regulation. Similarly, as seen in the treatment of cardiovascular diseases, monoclonal antibodies can significantly reduce the levels of key mediators of disease, such as increased levels of low-density lipoprotein cholesterol. In many ways, monoclonal antibody-based therapies are achieving the vision of “magic bullets” first articulated in 1900 by Nobel laureate Paul Ehrlich, the founder of chemotherapy, in that they directly target specific cell structural determinants and processes that cause disease in the body without harming healthy tissues.

Since the first therapeutic mAb was licensed more than 30 years ago, the field of monoclonal antibody development has advanced exponentially. Extensive progress has been made by using mAbs to treat non-communicable diseases, including cancer, cardiovascular disease, chronic respiratory conditions and diabetes, which are the leading...
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The vast majority of the now more than 100 licensed mAbs are for non-communicable diseases. Nowhere is the impact of mAb therapy more evident than for cancer. The use of mAbs has transformed the treatment of multiple cancers, some of which were previously difficult, or even impossible, to treat.

More than 100 years ago, Dr William Coley hypothesised that stimulating the immune system could cause cancers to regress. At the time his theory was largely dismissed. But today’s successful cancer immunotherapies are revolutionising cancer treatment.

Several licensed mAbs work by directly targeting proteins over-expressed on cancer cells and flagging these cells for destruction by the immune system. Another class of immunotherapies, referred to as checkpoint inhibitors, work by augmenting the body’s natural immune response to cancer.

Checkpoint inhibitors, either alone or in combination, have been effective in blocking cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death 1 (PD-1) receptor – two proteins on immune cells that suppress the immune response. Scientists James Allison and Tasuku Honjo received the 2018 Nobel Prize in Physiology or Medicine for discovering the function of CTLA-4 and PD-1 and the realisation that blocking these proteins enables the immune system to kill tumors more effectively.

Some recently approved mAbs such as Keytruda® and Tecentriq® work by binding specifically to the PD-1 receptor protein that is expressed on immune cells, or the PD-L1 ligand that is expressed on cancer cells. Such mAb-specific interactions prevent the PD-L1 ligand from binding to the PD-1 receptor. In healthy individuals, the interaction between PD-L1 and PD-1 suppresses the immune system to prevent an overactive immune response, which can be harmful. But with cancer, antibodies that block the interaction between PD-1 and PD-L1 actually stimulate the immune system to attack and destroy cancerous cells (and overcome the immune inhibitory effects that many cancers exhibit as a means of avoiding host immune clearance).

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Monoclonal antibodies for infectious/neglected diseases and drug-resistant bacteria

The use of mAbs to treat and prevent infectious/neglected diseases is a more nascent field than mAb development for non-communicable diseases. However, there is a large and growing pipeline of mAb candidates in development to both treat and prevent a wide range of infectious and neglected diseases including HIV, tuberculosis, Ebola, respiratory syncytial virus, influenza, malaria and COVID-19, as well as the growing threat of antimicrobial resistance (AMR). Antimicrobial resistance is of particular concern in low- and middle-income countries where the proportion of resistant infections ranges from 40 per cent to 60 per cent, as compared to an average of 17 per cent for the Organisation for Economic Cooperation and Development countries (Table 1, previous page).

Despite advances in modern medicine and healthcare, communicable diseases are still a leading cause of death in low-income countries. And, as the rapid emergence of the COVID-19 pandemic has shown, no country is immune to the effects of emerging infectious diseases.

Vaccines are in development for many viral and bacterial diseases, as well as for priority AMR pathogens (Table 2), but mAbs are a promising new approach for preventing and treating infectious diseases. Monoclonal antibodies have several advantages: they can target vulnerable epitopes on pathogens because of their exquisite specificity; they often exhibit excellent tolerability; they can be rapidly isolated, optimised and manufactured and they can provide rapid protection against infection.

Monoclonal antibody isolation and development efforts began rapidly following the emergence of COVID-19. The pace at which antibodies that neutralise SARS-CoV-2 have been isolated, characterised and advanced into clinical trials to evaluate their therapeutic and prophylactic efficacy demonstrates how quickly antibodies can be developed and manufactured in preparation for and response to emerging or existing infectious diseases.
References

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