Arch Argent Pediatr. 2025;e202510829

The continued relevance of monoclonal antibodies

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Fifty years ago, in August 1975, César Milstein and Georges Köhler published their work "Continuous cultures of fused cells secreting antibody of predefined specificity" in the journal *Nature*.[1] In it, they described how, by producing hybrids between cells from a murine myeloma and spleen cells from mice immunized against sheep red blood cells, they obtained a cell line producing large quantities of specific monoclonal antibodies (mAbs). This observation was quickly integrated into lines of research seeking to produce antisera against different antigens, such as histocompatibility system antigens and human tumor-associated antigens.[2]

The possibility of producing specific antibodies on a large scale using the technique described by Köhler and Milstein was the starting point for the development of numerous methods used for the diagnosis and treatment of acute and chronic diseases that cause disability and death, such as infectious diseases, autoimmune diseases, and cancer.

In a short time, specific drugs for diseases or groups of diseases with similar etiopathogenesis began to be developed. For example, autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, psoriasis, Crohn's disease, and myasthenia gravis are triggered by the dysregulation and proliferation of B lymphocytes that produce cytokines such as interleukins or tumor necrosis factor (TNF), which cause tissue damage.[3]

Clinical trials have shown that the autoaggression process can be controlled by administering mAb specifically targeted against these cytokines.

Due to their production from living cells, these products are considered "biological" drugs, such as vaccines, blood components, or gene therapy.

The first drug to be developed was rituximab, an anti-B lymphocyte mAb that binds to the CD20 protein on the lymphocyte membrane and induces apoptosis. Another widely used drug, infliximab, is a direct inhibitor of TNF. Tocilizumab is a humanized mAb against the interleukin-6 receptor.

The patient's immune system may generate a rejection response against mAbs of murine origin and, over time, reduce their effectiveness. In 1988, Greg Winter and colleagues published their technique for producing humanized hybrid antibodies, delaying (though not eliminating) the possibility of recognition and destruction by the recipient organism.[4]

The name of mAbs includes parts of the words that designate their structure and function. For

doi: http://dx.doi.org/10.5546/aap.2025-10829.eng

To cite: Rodríguez MS. The continued relevance of monoclonal antibodies. *Arch Argent Pediatr.* 2025;e202510829. Online ahead of print 28-AUG-2025.

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example, RITUXIMAB: RI (name chosen by the manufacturer) + TU (therapeutic target: tumor) + XI (chimeric origin) + MAB (monoclonal antibody); or PALIVIZUMAB: PALI (name chosen by the manufacturer) + VI (therapeutic target: virus) + ZU (humanized) + MAB (monoclonal antibody).

More than 100 mAbs for the treatment of autoimmune diseases, cancer, and inflammatory diseases have already been approved by the US Food and Drug Administration (FDA).

Among the mAbs approved in Argentina by ANMAT (National Administration of Medicines, Food, and Medical Technology) for pediatric use are palivizumab, for prophylaxis of respiratory syncytial virus infection in high-risk children, rituximab for non-Hodgkin's lymphoma, infliximab for Crohn's disease and rheumatoid arthritis, and basiliximab for the prophylaxis of acute kidney transplant rejection.

For cancer treatment, the therapeutic effectiveness of mAbs was expanded by conjugating them with cytotoxic drugs, toxins, or radionuclides. These conjugated antibodies have three components: an mAb specifically targeting a tumor cell surface antigen, a highly efficient cytotoxic drug called a payload, and a substance that binds them together (linker) and releases the drug upon contact with the tumor antigen. This limits the systemic toxicity of the chemotherapeutic agents and increases their affinity for tumor cells.[5,6]

These monoclonal antibody conjugates (mAcs) have become the most widely studied and approved drugs in recent years due to their benefits in the treatment of hematological cancers and solid tumors, as well as autoimmune and viral diseases.

There are more than 50 mAcs in clinical trials as monotherapy and in combination with other chemotherapeutic agents to treat different types of cancer.

Their use spread and was implemented so quickly that, in many cases, we became familiar with the name of the product and the disease for which it is indicated without knowing exactly how it works.

The existence of these new treatments forced a redefinition and reclassification of diseases, especially different types of tumors, according to their antigenic and genetic characterization (in the latter case, as targets for other therapies also under development, such as molecular therapy).

Biological products are expensive due to the high costs of their development and manufacture. To reduce costs, several regulatory agencies have approved the production and use of "biosimilars", biological drugs that are not identical copies but can be interchangeable with the reference product and produce the same clinical result. For biosimilars, the risk-benefit profile is established with evidence demonstrating biosimilarity with the reference product, comparative clinical efficacy trials that serve a confirmatory role, and highly sensitive analytical methods to detect possible differences from the original product. This significantly reduces the time and especially the resources needed for their development.[7]

Unfortunately, the effectiveness of these new treatments to control or cure serious diseases by changing their historical prognosis faces major limitations. On the one hand, not all professionals are aware of these pharmaceutical advances, and their patients will not have timely access to the benefits. On the other hand, there are significant disparities in the population's ability to obtain quality healthcare that provides early diagnosis and timely treatment. The fragmented health system, involving multiple actors, does not facilitate the delivery of these costly treatments to all those who need them.

Integration between different levels of health care and the virtuous participation of the state and industry are essential to guarantee universal access to these life-saving treatments.

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