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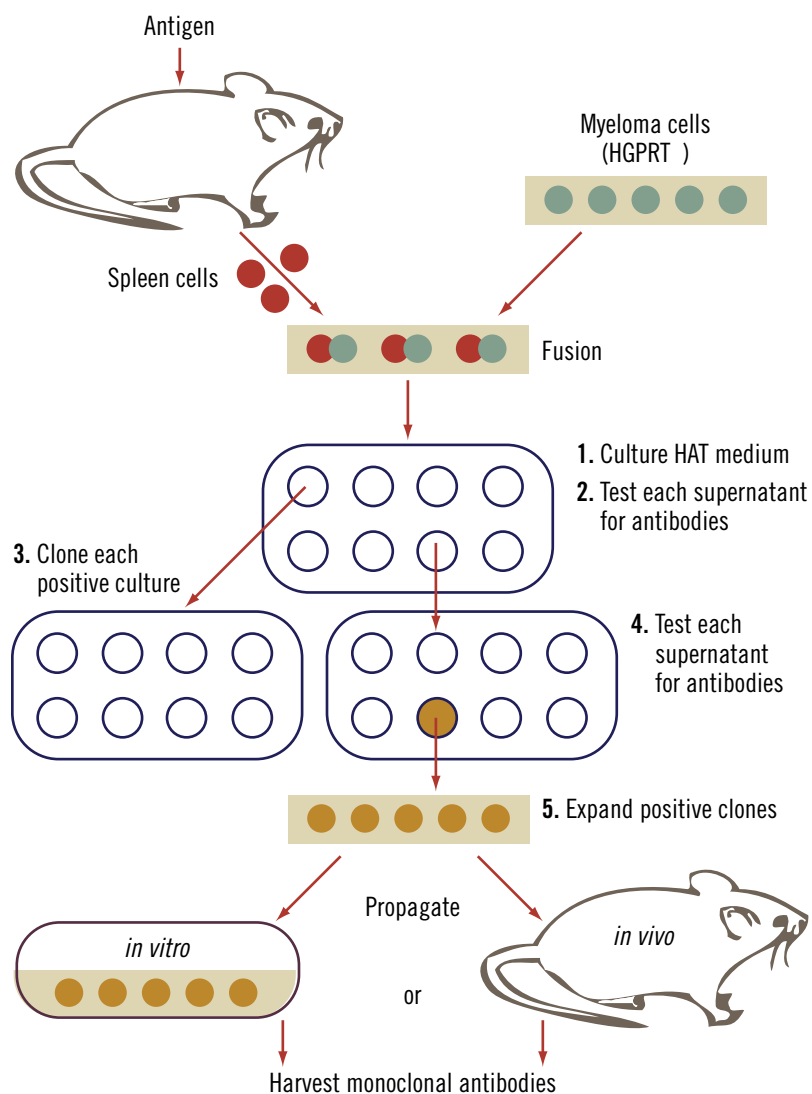
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Figure 2.1. Monoclonal Antibody Production



Source: Kimball's Biology Pages. <http://biology-pages.info>

Murine-Derived Monoclonal Antibodies

The pivotal moment in the history of applied antibody use came in 1975, with the invention of a method for creating pure and specific populations of monoclonal antibodies. Georges Köhler, PhD, and César Milstein, PhD, pioneered this method, working at the UK Medical Research Council's Laboratory of Molecular Biology in Cambridge.² They were awarded a Nobel Prize for this work in 1984.

The process typically starts with the injection of the antigenic protein into a mouse (Figure 2.1). The mouse's immune system recognizes the protein as foreign, and some of its B cells begin producing an appropriate antibody. B cells are then extracted from the animal's spleen and, to achieve longevity in culture, added to myeloma cells. The two cell types fuse into hybridomas. Each hybridoma is then cultured and screened against the epitope of the desired antibody. Nonreactive fused cells are discarded, while those that produce the correct antibody are isolated and can be cultured indefinitely.

The first generation of mAbs were murine (derived from mice), but these were soon discovered to pose several new problems. The human immune system recognizes such an antibody as foreign and raises a human anti-mouse antibody, or HAMA, response to it. This results in the mouse mAb being rapidly neutralized and renders subsequent patient treatments with the mAb ineffective. The HAMA response also induces the formation of immune complexes that can damage the kidneys.

The first mAb approved by the US Food and Drug Administration (FDA) was muromonab-CD3 (Orthoclone OKT3), a murine antibody for treating organ rejection in patients who have received kidney, heart, and liver transplants. Despite being a mouse antibody, it can be used repeatedly, because this patient population is taking immunosuppressive drugs as well to reduce the risk of rejection, which also serves to also quell the HAMA response. In addition, because of their foreignness, mouse antibodies

Menarini Group

Menarini (Florence, Italy) is conducting Phase III development of abagovomab (formerly ACA125), a murine anti-idiotypic mAb originally developed by CellControl Biomedical Laboratories, a German firm, for ovarian cancer. The drug functionally mimics the CA125 antigen, inducing humoral and cellular anti-CA125 immunity. It is different from United Therapeutics' (Silver Spring, MD) OvaRex (oregovomab), which binds circulating CA125, at which point the antibody-antigen complex reprograms the immune system to recognize the antigen as foreign and triggers an immune response against both antigen and tumor. (OvaRex was dropped from development in late 2007 after it failed to provide a significant benefit in Phase III trials.) In a Phase II trial in patients with advanced ovarian cancer in whom standard therapies had proved ineffective, treatment with abagovomab elicited a specific anti-idiotypic antibody response in 68.1% of patients; in that subgroup, median survival time was 23.4 months, compared with 4.9 months for nonresponders.²⁸ In December 2006, Menarini initiated an international Phase III trial called MIMOSA (Monoclonal Antibody Immunotherapy for Malignancies of the Ovary by Subcutaneous Abagovomab) to evaluate the mAb as maintenance therapy in 870 patients with ovarian cancer who achieved complete responses with first-line chemotherapy. Results are expected in 2010.

Onyvax

Onyvax's (London, UK) Onyvax-105 (105AD7) is a human anti-idiotypic mAb that mimics CD55, an antigen overexpressed on many cancer types that is believed to protect tumor cells from immune attack. Phase I trials in colorectal cancer and pediatric osteosarcoma have been completed, and Onyvax is using the results to further develop a second-generation antibody to enter preclinical studies.

Conjugated Monoclonal Antibodies for Cancer

One popular approach to increasing the potency of antibodies is to use their target specificity to deliver therapeutic payloads to target cells, typically cancer cells. Here, mAbs are tagged with a toxic substance such as a radioisotope, a toxin, or a small-molecule therapeutic, which assumes the usual duties of the effector system by killing the target cell. More information on the different types of conjugates can be found in Section 2.5. Three mAbs on the market fall into this category: Mylotarg, a humanized anti-CD33 antibody conjugated to calicheamicin for acute myeloid leukemia, and Zevalin and Bexxar, radiolabeled murine anti-CD20 antibodies for NHL. Table 3.3 lists 34 conjugated mAbs in clinical trials.

Table 3.3 Conjugated Monoclonal Antibodies in Clinical Trials for Cancer

Company	Product	Type	Indication	Status
Actinium Pharmaceuticals (Florham Park, NJ)	HuM195-Ac-225	Humanized anti-CD33 mAb (M195) conjugated to actinium 225	AML	Phase I
Actinium Pharmaceuticals	HuM195-Bi-213	Humanized anti-CD33 mAb (M195) conjugated to bismuth 213	AML	Phase II