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Human monoclonal antibodies in the clinic: Novel insights into the choice of specific targets

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The use of therapeutic antibodies made a great stride when Köhler and Milstein introduced the hybridoma method. Monoclonal antibodies derived from deliberate immunization of mice were not applicable to patients, whereas humanization of these antibodies rendered them pertinent. The Epstein-Barr virus (EBV) method, which was the first to generate human monoclonal antibodies, signified a new approach. It was aimed to produce monoclonal antibodies mirroring the human antibody repertoire and presumably reflecting those that *in vivo* successfully coped with pathogens, toxins, tumor cells, etc. This very same approach has been extended to the production of human monoclonal antibodies by applying molecular methods in conjunction with single B cell methodologies. Accordingly, antibodies against a variety of antigens (i.e., pathogens, amyloid β) were developed from healthy individuals. Recently, a dramatic change took place in the field of oncology, related to the type of target chosen for therapeutic human monoclonal antibodies. Whereas in the past chimeric and humanized antibodies were prepared against presumably tumor antigens, today pharmaceutical companies are investing much effort in creating antibodies directed against signaling receptors on the surface of T cells and tumor cells. Human monoclonal antibodies targeting CTLA-4/ B7, PD-1/PDL-1, CEACAM-1 cell surface molecules are novel promising means to cope with cancer cells. The development of molecular chimeric antigen receptor (CAR) constructs to arm autologous T cells against target tumor antigens is an additional and encouraging clinical venue for human monoclonal agonist antibodies. However, the latter approach suffers from its dependence on the independent production of xenogeneic monoclonal antibodies against tumor-specific antigens. Patients who spontaneously have recovered from cancer, patients with autoimmune diseases and healthy individuals who display protective antibodies against signaling molecules and against other antigens, could be sources for therapeutic human monoclonal antibodies. Such antibodies, similar to those obtained by the original EBV method, would mirror the clinically-effective antibody repertoire of naturally immunized individuals, rather than that of artificially immunized mice.

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