NANOBODIES: UNIQUE BIOLOGICAL MODALITIES TO TREAT DISEASES

Nanobodies are unique single domain antibodies that are expressed in camels, alpacas, llamas and other camelid animals. These tiny antibodies are about 10% the size of regular antibodies and have a mass of about 15 kDa and due to their small size, they were named nano-antibodies or nanobodies. They were discovered in the 1980s and were found to contain only a single variable domain of the antibody heavy chain[1]. The single variable domain contains an antigen binding site and is considered to be the smallest functional antibody fragment discovered so far. Nanobodies have been found to have desirable biophysical characteristics such as prolonged shelf life, resistance to heat, chemical or proteolytic degradation, effective tissue penetration and low immunogenicity[2]. Additionally, there are reports that nanobodies can refold into functional conformations after heat denaturation[2] but this is currently under debate. Nanobodies have a unique structure where they form a finger-shaped loop that can penetrate the antigen binding site or active site of an enzyme target. In contrast, conventional antibodies form a cup shaped structure that may not bind directly to the target site on the antigen[3]. Initially, scientists developed nanobodies by immunizing llamas and other camelids and then screening their sera for target nanobodies. However, this method had limited success and was very expensive and time consuming. Additionally, access to large animal facilities for immunization and collection were limited. However, scientists at Harvard developed a yeast-based system to express nanobodies thus avoiding the need to immunize large animals[4]. Nanobodies have relatively simple monomeric structures that are not post-translationally modified allowing for scalable expression in bacterial or yeast systems at milligram per liter levels. The low-cost manufacturing process that produces reproducible levels of nanobodies is highly desirable for therapeutic antibody manufacturing[2]. Due to the small size of nanobodies, they can be delivered using multiple methods including aerosols, which can help broaden patient access to the therapies.

Nanobodies received a lot of interest as a therapeutic modality when the first nanobody therapeutic was approved in 2019[5] by the European Medicine Agency (EMA) and FDA. Caplacizumab was the first nanobody based therapeutic that was initially developed by Ablynx, which was then acquired by Sanofi[5]. The FDA approved caplacizumab for the treatment of acquired thrombotic thrombocytopenic purpura (aTTP), a rare clotting disease[5]. aTTP causes a disruption in the clotting cascade resulting in the formation of large multimers of the von Willebrand factor protein that bind to platelets forming clots or thrombi that result in emboli and other complications. Caplacizumab binds to the von Willebrand factor protein at a specific site and prevents the formation of the large multimers that cause clots and emboli.

The global SARS-CoV2 pandemic has triggered frantic efforts to find a cure for the disease that has resulted in millions of deaths. Currently, three monoclonal antibody based therapeutic regimens have received Emergency Use Authorizations (EUA) from the FDA for use in mild to moderate cases[6]. However, these antibodies are effective during a short time window in the early stages of infection and administering the therapies have significant logistical challenges[7]. Therefore, there is a strong clinical need for effective therapies that can be manufactured rapidly in a cost-effective manner and have optimal stability with minimal lot to lot variation. Nanobodies are a viable option as a therapeutic for SARS-CoV2 and recently, a group of US and EU scientists developed nanobodies targeting the SARS-CoV2 spike protein[8]. They developed a biparatopic nanobody which recognizes two distinct regions in the spike protein that can be delivered using an aerosol directly into the lungs of infected patients to inhibit viral infection. The researchers engineered nanobodies that neutralized the spike protein binding to the cell receptor via a unique mechanism. The nanobodies bound to the inactive SARS-CoV2 spike protein to induce a conformational change that resulted in premature inactivation of the spike protein. In other words, the nanobodies caused a change in the spike protein structure which prevented the virus from binding to and infecting cells[8]. These results suggest that engineered nanobodies could be the therapeutic answer to manage the pandemic that has ravaged the world.

References:

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