DDN EXPLORING DRUG DISCOVERY AND DEVELOPMENT

IMMUNOTHERAPY FOR INFECTIOUS DISEASES

Humans are surrounded by pathogenic assaults, from bacteria that lurk on surfaces, to airborne viruses that infect the respiratory system. As the world grapples with the ongoing pandemic, researchers focus on the body's first line of defense: the immune system. Immunotherapy is typically thought of in the context of cancer treatment, but many of the same therapies used to activate the immune system to treat cancer may also combat infectious diseases. These therapies fall into three broad categories: engineered T cells, therapeutic antibodies, and the activation of endogenous T cells.[1]

Therapeutic Monoclonal Antibodies

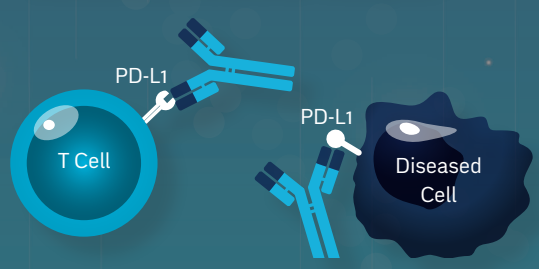
Therapeutic antibodies are perhaps the most versatile immunotherapy treatment. Researchers use vaccines to supply therapeutic antibodies, or stimulate the production of therapeutic antibodies through various mechanisms, including introducing a dead or attenuated virus, or the RNA sequence for a viral protein.[1] Monoclonal antibodies have neutralized the Zika virus, Ebola virus, and in some cases SARS-CoV-2, and are considered the treatment of choice for many bacterial pathogens.[6,7,8,9]

Monoclonal antibodies neutralize antigens on the surface of viral and bacterial pathogens.

Molecular engineers may conjugate monoclonal antibodies with small molecules toxins and other biological agents to ensure their targeted delivery and efficiency.

Checkpoint Inhibition

Similar to cancer cells, dysfunctional T cells infected with *Mycobacterium tuberculosis* aberrantly express inhibitory receptors such as PD-1 and PD-L1. These receptors bind to functioning T cells and dampen their ability to recognize and destroy diseased cells. Checkpoint inhibition therapy administers antibodies that bind to these inhibitory signals, allowing T cells to identify infected cells. While revolutionary for cancer, checkpoint inhibition for infectious disease is still under investigation.[10,11]

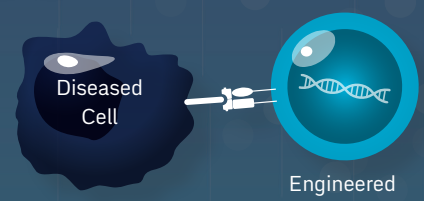


Cytokines

Physicians administer proinflammatory cytokines to activate T cells capable of destroying pathogens. However, with SARS-CoV-2 infection, macrophages and T cells may produce too many cytokines, resulting in a cytokine storm. In such cases, physicians administer immunomodulatory drugs such as Tocilizumab to decrease cytokine production.[2]

Engineered T Cells

Researchers genetically modify patient-derived T cells to express chimeric antigen receptors (CARs) and return them intravenously into the body, where they preferentially target specific pathogens. Bi- and tri-specific CARs prevent HIV infection while efficiently killing HIV-positive cells in mouse models.[3] CARs specific to cytomegalovirus (CMV) have also been described.[4] Two ongoing clinical trials are exploring the ability of CAR T cell therapy to eradicate latent HIV reservoirs in humans.[1] Researchers may also use adoptive cell transfer, where they manipulate and expand T cells ex vivo to combat the Zika virus.[5]



Bispecific Antibodies

Bispecific antibodies bind two separate targets, an antigen on the diseased cell and an antigen, such as CD3, on a cytotoxic T cell. By binding both antigens, bispecific antibodies bring diseased cells into proximity with immune effector cells, where they can be promptly eliminated. Researchers engineered a bispecific antibody that neutralizes the Zika virus and prevents the generation of resistant mutant strains.[6] Clinical trials investigating the ability of engineered bispecific antibodies for *Pseudomonas aeruginosa* and *Staphylococcus aureus* bacterial pathogens are also underway. Such treatments may prevent bacterial pneumonia in high-risk patients.[12,13,14]

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