IMMUNOTHERAPY

Three targets are better than two

Nat. Cancer **1**, 86–98 (2020)

Bispecific antibodies used in cancer therapy function by triggering T cells' cytotoxic activity and bringing them into apposition with cancer cells. In *Nature Cancer*, Gary Nabel and colleagues take the basic format of a bispecific antibody and add a third target. Their chimeric recombinant antibody consists of one arm that targets CD38 on the cancer cell, in this case a multiple myeloma cell, and the second arm is split to recognize two distinct targets on T cells — CD3 and CD28. While CD3 is essential for triggering the T cell, the additional simultaneous binding of CD28 allows for full activation and protection from activation-induced cell death. In vitro assays demonstrate that the trispecific antibody is superior to its bispecific counterpart in killing myeloma cell lines. A concern with potentially superagonistic anti-CD28 antibodies is the possibility of overactivating the T cells and causing a life-threatening cytokine release syndrome; however, the authors' initial toxicity studies in non-human primate models show no overt adverse events, especially when the trimeric antibody is injected subcutaneously. Finally, the trimeric antibody was able to suppress cancer growth in a humanized mouse model of multiple myeloma. *ZF*

https://doi.org/10.1038/s41590-020-00851-8

NEUROIMMUNOLOGY

The vagaries of control revealed

Proc. Natl Acad. Sci. USA **117**, 29803–29810 (2020)

The vagus nerve, originating from the brain stem, can exert potent modulatory effects on systemic immune responses via a mechanism termed the 'inflammatory reflex.' In the *Proceedings of the National Academy of Sciences*, Kevin Tracey and colleagues use a combination of anatomical functional mapping and nerve manipulation via optogenetics to understand the neuroanatomy of the inflammatory reflex. They identify a brain stem region known as the dorsal motor nucleus (DMN), which projects cholinergic neurons via the vagus nerve and terminates in proximity to splenic nerve bodies. Optogenetic stimulation of the DMN invokes action potentials in the splenic nerve and inhibits tumor necrosis factor production and endotoxemia induced by lipopolysaccharide injection. These results reveal that a discrete region of the brain stem can exert active control over the innate immune response. *ZF*

https://doi.org/10.1038/s41590-020-00852-7

COVID-19

Durable memories

Cell https://doi.org/10.1016/j.cell.2020.11.029 (2020)

Since the recent onset of the COVID-19 pandemic, there have been some reports of suspected cases of reinfection by SARS-CoV-2. The question remains, however, of whether SARS-CoV-2 viral infection can elicit durable immunologic memory responses or whether memory generation is somehow impeded by viral virulence mechanisms. In *Cell*, Rodda et al. report a longitudinal analysis of adaptive immune memory that had arisen in patients who had experienced mild COVID-19 disease and had recovered. Blood samples taken at 1 and 3 months post-symptom onset contain circulating antibodies specific for the receptor-binding domain (RBD) of the SARS-CoV-2 spike (S) protein, which are capable of inhibiting the interaction with the host ACE2 viral receptor, suggesting that long-lived plasma cells had been generated. RBD-specific memory B cells, identified by tetramer enrichment, are present in convalescent blood and increased in frequency at the later time point. Monoclonal antibodies generated from a subset of these memory B cells are capable of blocking the RBD–ACE2 interaction and neutralizing the virus. Likewise, at 3 months post-infection, patients who have recovered harbor S-specific memory $CD8^+$ and $CD4^+$ T cells, including circulating $CXCR5^+$ follicular helper T cells and $CXCR3^+$ central memory T cells, that respond to restimulation by proliferating and producing cytokines. Thus, durable adaptive memory can arise in response to community-acquired SARS-CoV-2 infection and can potentially provide protection to secondary exposure. *LAD*

https://doi.org/10.1038/s41590-020-00853-6

COVID-19

SARS-CoV-2 neuroinvasion

Nat. Neurosci. https://doi.org/10.1038/s41593-020-00758-5 (2020)

A common symptom reported by COVID-19 patients is the loss of taste and smell, suggesting that SARS-CoV-2 infection might also affect cells within the central nervous system (CNS). In *Nature Neuroscience*, Meinhardt et al. show that SARS-CoV-2 virions, RNA and spike protein are readily detectable in nasopharyngeal tissue obtained upon autopsy of deceased patients who had COVID-19. In particular, olfactory sensory neurons in proximity to infected mucosal epithelial cells can become infected, leading to retrograde transport of virions through the cribriform plate into the CNS. The presence of SARS-CoV-2 in the CNS correlates with microglial expression of HLA-DR and the presence of inflammatory cytokines. Higher viral loads correlate with higher detection frequencies in other neuronal cells, including those found in the olfactory bulb and medulla oblongata, a neuroanatomical region that controls respiratory and cardiovascular functions. Some patients also displayed neurovascular tissue damage, evidenced by microthrombotic lesions and infarcted tissue. These findings suggest that direct infection of the CNS by SARS-CoV-2 contributes to the pathology observed in patients with acute infection. *LAD*

https://doi.org/10.1038/s41590-020-00854-5

Laurie A. Dempsey and Zoltan Fehervari