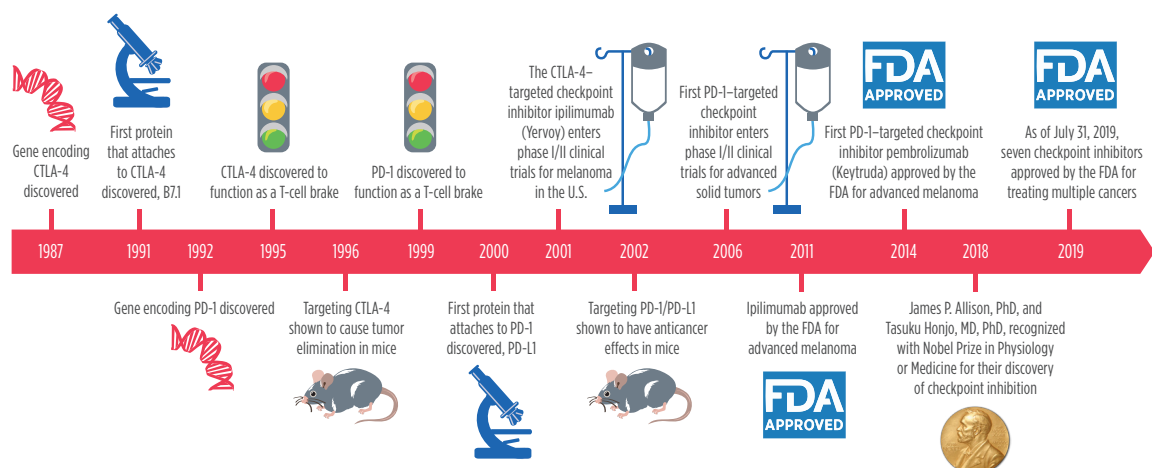


FIGURE 14

STOPS ALONG THE WAY TO DEVELOPING CHECKPOINT INHIBITORS



Checkpoint inhibitors are cancer immunotherapeutics that work by releasing “brakes” called immune checkpoint proteins on the surface of cancer-fighting immune cells called T cells. The first checkpoint inhibitor to be approved by the U.S. Food and Drug Administration (FDA) was ipilimumab (Yervoy), in March 2011. Ipilimumab targets an immune-checkpoint protein on T cells called CTLA-4. Several other checkpoint inhibitors target a second immune checkpoint protein called PD-1. The first of these immunotherapeutics to be approved by the FDA was pembrolizumab (Keytruda), in September 2014. More than 20 years of basic and clinical research underpinned the development of ipilimumab and pembrolizumab, starting with the discoveries of the

CTLA-4 and PD-1 genes in 1987 and 1992, respectively (236)(237). Other basic research milestones along the way to the FDA approvals include the identification of the brake function of CTLA-4 and PD-1 (238-240), the identification of the proteins that attach to and trigger the brake function of CTLA-4 and PD-1 (241)(242), and the demonstration that immunotherapeutics targeting these brakes can protect them from being triggered (237)(243). Two researchers whose pioneering work established the paradigm of checkpoint inhibitors, James P. Allison, PhD, and Tasuku Honjo, MD, PhD, were recognized with the 2018 Nobel Prize in Physiology or Medicine for “their discovery of cancer therapy by inhibition of negative immune regulation.

Adapted from (244)