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If you build it, they will come: Reaching across the “IL” with Neo-2/15

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Abstract

A computationally designed mimic of interleukin-2 (IL-2) selectively expands cytotoxic CD8+ T cells over regulatory T cells and supports antitumor immunity.

Interleukin-2 (IL-2) is a critical cytokine for both cytotoxic and (at lower doses) regulatory lymphocyte activation through IL-2 receptor α [IL-2R α (also known as CD25)]. However, substantial clinical toxicities have been associated with high-dose IL-2 treatment. Novel approaches to circumvent this problem in anticancer immunotherapy include targeting IL-15. IL-15, which activates and sustains survival of multiple cytotoxic lymphocyte subsets, shares the IL-2R β chain and common gamma chain heterodimer (IL-2R $\beta\gamma$ c) with IL-2 but requires a distinct receptor α subcomponent—IL-15R α . The authors used a novel computational approach to design an IL-2 structural mimic [neoleukin-2/15 (Neo-2/15)] lacking the CD25 binding site but capable of binding IL-2R $\beta\gamma$ c. This reengineered protein structure improved upon the affinity and heat stability of the natural cytokine, optimizing IL-2 functional activation while simultaneously potentially mitigating the major off-target toxicities seen with IL-2.

The authors demonstrate that Neo-2/15 treatment preferentially expanded cytotoxic CD8+ T cells over T regulatory cells. Even more promising, Neo-2/15 supported tumor control and survival either as a lone therapeutic agent or in combination with antibody-based or chimeric antigen receptor (CAR) T cell therapy. Another important limitation of engineered immunotherapies is the potential to develop a neutralizing immune response to endogenous (physiologic) cytokines. The authors addressed this by demonstrating that neutralizing antibodies to Neo-2/15 do not cross-react with endogenous IL-2 (presumably because Neo-2/15 structure differs substantially from that of native IL-2).

These studies provide a key proof of principle that computational design of therapeutics can be extended to bioactive proteins. They also demonstrate that, by reengineering the native structure, it is possible to retain or modify bioactivity of cytokines while editing out sections that reduce stability. These approaches hold important translational potential for next-

generation therapeutics by allowing redesign of complex molecules that combine the salutary properties of immune signaling molecules while editing out undesirable side effects.

Highlighted Article

De novo design of potent and selective mimics of IL-2 and IL-15. *Nature* 565, 186–191 (2019).
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