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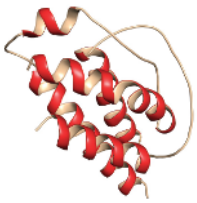
Drug Design

Major finding: A *de novo* IL2/IL15 mimic has improved antitumor activity and reduced toxicity compared with native IL2.

Concept: Design of a hyperstable mimic that binds IL2Rβγc but not IL2Rα avoids challenges of IL2 variants.

Impact: This approach may be broadly useful for enhancing efficacy and reducing toxicity of biologically active molecules.

DE NOVO CYTOKINE MIMICS HAVE IMPROVED THERAPEUTIC PROPERTIES



Recombinant interleukin-2 (IL2) is an effective immunotherapy in several human cancers, but its high toxicity and tendency to induce the proliferation of immunosuppressive regulatory T cells (Treg) has limited its broader clinical use. Approaches to improve the therapeutic properties of IL2 have typically involved mutating or modifying the naturally occurring protein to reduce its interaction with IL2 receptor alpha (IL2Rα), but such approaches cannot completely eliminate IL2Rα binding, often result in reduced stability and potency, and carry the risk of inducing immune responses that cross-react with endogenous IL2. To circumvent shortcomings associated with incremental mutation or modifications of native IL2, Silva and colleagues developed a computational *de novo* protein design method wherein an idealized, stable globular protein structure without an IL2Rα interaction surface was built around the known IL2/IL15–IL2Rβγc interaction surface. Several rounds of optimization for stability and high IL2Rβγc affinity led to the development of Neo-2/15, a *de novo* IL2/IL15 mimic with little sequence identity to native IL2. Neo-2/15 has a higher affinity for IL2Rβγc and is significantly more stable than native IL2 or the IL2 variant super-2. Neo-2/15 also more potently activated T cells *in vitro*, led to reduced expansion of Tregs *in vivo*, and was not immunogenic. Neo-2/15 significantly delayed tumor growth and extended survival alone or in combination without the toxicity seen with native IL2, and led to a significant increase in intratumoral CD8:Treg ratios. This approach to *de novo* protein design thus has the potential to lead to safer, more effective IL2-based immunotherapy and can potentially be used to improve the therapeutic properties of other proteins. ■

Silva DA, Yu S, Ulge UY, Spangler JB, Jude KM, Labão-Almeida C, et al. De novo design of potent and selective mimics of IL-2 and IL-15. Nature 2019;565:186–91.

Leukemia

Major finding: Targeting a mutant NPM1-derived neoantigen has antitumor activity against AML cells.

Concept: *NPM1* mutations create a C-terminal alternative reading frame not present in normal blood cells.

Impact: *NPM1*-mutant AML may be a candidate for neoantigen vaccines or adoptive T-cell therapy.

NPM1 MUTATIONS CREATE A TARGETABLE SHARED NEOANTIGEN IN AML

The majority of tumor neoantigens derive from patient-specific mutations and necessitate the development of personalized vaccine or autologous T-cell therapy approaches. The insertion mutations in nucleophosmin 1 (*NPM1*) that are found in 30% to 35% of acute myeloid leukemias (AML) result in longer mutant proteins with the same 11-amino acid C-terminal alternative reading frame (ΔNPM1), leading van der Lee and colleagues to hypothesize that the unique C terminus of ΔNPM1 might create neoantigens that could potentially be targeted by immunotherapy. Analysis of the peptides bound by HLA class I surface molecules in primary AMLs revealed that the ligandomes of 7 of 8 *NPM1*-mutant AMLs included peptides corresponding to the ΔNPM1 C terminus. T cells recognizing part of the ΔNPM1 C terminus could be isolated and expanded from large numbers of peripheral blood mononuclear cells, and these T cells had reactivity against *NPM1*-mutant AMLs. A TCR recognizing the ΔNPM1 C-terminal segment could be transduced into $CD4^+$ and $CD8^+$ T cells, and these transduced T cells had reactivity against all *NPM1*-mutant AML samples tested, indicating that TCR gene transfer can result in specific recognition of the endogenous ΔNPM1 C-terminal neoantigen. The TCR-transduced T cells also specifically induced lysis of primary human AML cells expressing ΔNPM1 but not wild-type NPM1 *in vitro* and significantly prolonged survival of immunodeficient mice engrafted with a human ΔNPM1-expressing AML cell line. These results demonstrate that ΔNPM1 creates a targetable neoantigen and, given the prevalence of *NPM1* mutations in AML, raise the possibility that it could potentially be an ideal target for "off-the-shelf" neoantigen vaccines or adoptive transfer of TCR-engineered T cells. ■

van der Lee DI, Reijmers RM, Honders MW, Hagedoorn RS, de Jong RC, Kester MG, et al. Mutated nucleophosmin 1 as immunotherapy target in acute myeloid leukemia. J Clin Invest 2019;129:774–85.

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AACR American Association for Cancer Research

CANCER DISCOVERY

De Novo Cytokine Mimics Have Improved Therapeutic Properties

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