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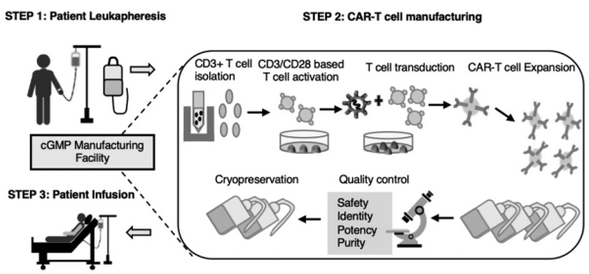
MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Selected Articles from This Issue

Anti-CD19 CAR with Favorable Efficacy to Toxicity Balance



Dwivedi *et al.* | Page 846

Chimeric antigen receptor (CAR) T cell therapy has shown great efficacy against CD19 positive hematological cancers. However, cytokine release syndrome (CRS) in patients treated with CD19 CAR-T cell therapy remains a significant toxicity to address. Dwivedi and colleagues developed a novel anti-CD19 CAR T cell containing a humanized framework region of scFv from a murine FMC63 monoclonal antibody. The humanized CAR T cell released significantly less cytokines (IFN-γ, TNF-α), reduced IL-6 induction from monocytes, and produced a more even CD4+ and CD8+ T cell distribution. Furthermore, CAR T cells eradicated NALM6 tumor burden in vivo. Taken together, these modified features might be beneficial for reducing toxicity of CAR T cells.

Discovery of JNJ-63576253, a Next-generation AR Antagonist

Branch *et al.* | Page 763

Mutations occurring in the ligand binding domain of the androgen receptor (AR) lead to therapy resistance. In particular, the AR F877L mutation leads to an antagonist-to-agonist switch in response to second-generation inhibitors such as enzalutamide and apalutamide. Branch and colleagues describe JNJ-63576253, a next-generation AR pathway inhibitor of wild-type, AR F877L, and other clinically detected ligand binding domain mutants. JNJ-63576253 inhibited downstream target gene expression of AR and impeded tumor growth in an enzalutamide-resistant F887L xenograft model. Their results support the ongoing Phase 2 clinical development of JNJ-63576253 (NCT02987829).

Novel IL15-based Immunocytokines

Corbellari *et al.* | Page 859

IL-2 and IL-15 are both able to stimulate the proliferation of T cells, promote the synthesis of immunoglobulin, and preserve the survival of NK cells. However, IL-2 also maintains peripheral regulatory T cells (Tregs), while IL-15 instead stimulates the survival of CD8+ memory T cells. In this manuscript, Corbellari and colleagues describe two IL-15-diabody fusions with the F8 antibody (F8-F8-IL-15 and F8-F8-SD-IL-15). These antibody-interleukin-15 fusion proteins showed favorable distribution profiles and displayed potent anti-cancer activity in a mouse model of lung metastasis. These studies reinforce the many clinical studies investigating the use of targeted IL-15 therapies.

Shaping Functional Avidity and the Pivotal Regulatory Role of CAR Down-modulation

Greenman *et al.* | Page 872 and Page 946

In two related manuscripts Greenman, Pizam, and colleagues performed an extensive study of the functional significance of the biophysical properties of chimeric antigen receptor engineered T cells (CAR T cells). They generated an experimental system in which affinity, avidity and antigen density are controllable within a single experimental model of a specific HLA-peptide complex targeted with TCR-like antibodies of single defined specificity. In the second manuscript they built an evolving phenotypic model of CAR T-cell regulation, which suggested that receptor down-modulation is a key determinant of CAR T-cell function. These results have a potential to predict and therefore advance the rational design of CAR T-cell therapy.

Molecular Cancer Therapeutics

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