A Novel Alpha-Active IL-2-Fc Has Expanded Therapeutic Index And Robust Monotherapy Efficacy In Mouse Cancer Models And Strong Synergy With PD-1 Blockade

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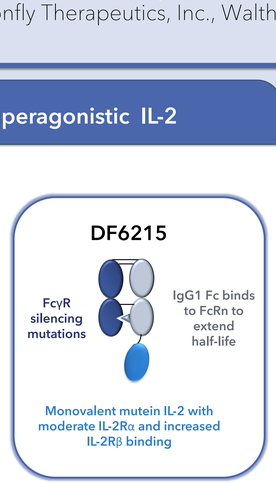
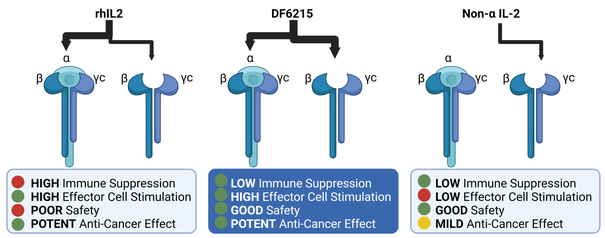
DF6215: Alpha-Active Superagonistic IL-2

IL-2 stimulates potent tumor immunity. Aldesleukin is an approved recombinant human IL-2; however, its short half-life necessitates frequent dosing, and toxicity requires 5 days of hospitalization each treatment cycle, limiting aldesleukin's clinical use. To reduce toxicity, IL-2 agonists were created with abolished binding to IL-2Rα, but these non-α IL-2s also had diminished clinical efficacy.

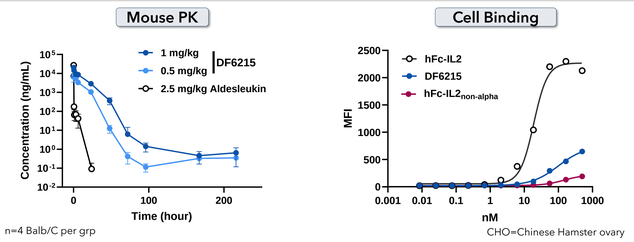
DF6215 maintains IL-2Rα binding but with reduced affinity and has increased IL-2Rβγ stimulation to improve the benefit-to-risk ratio compared to historic IL-2 drugs.



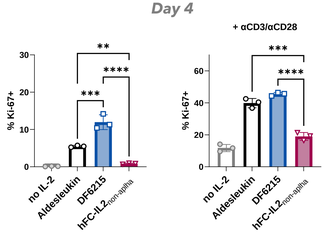


Images created with BioRender.com

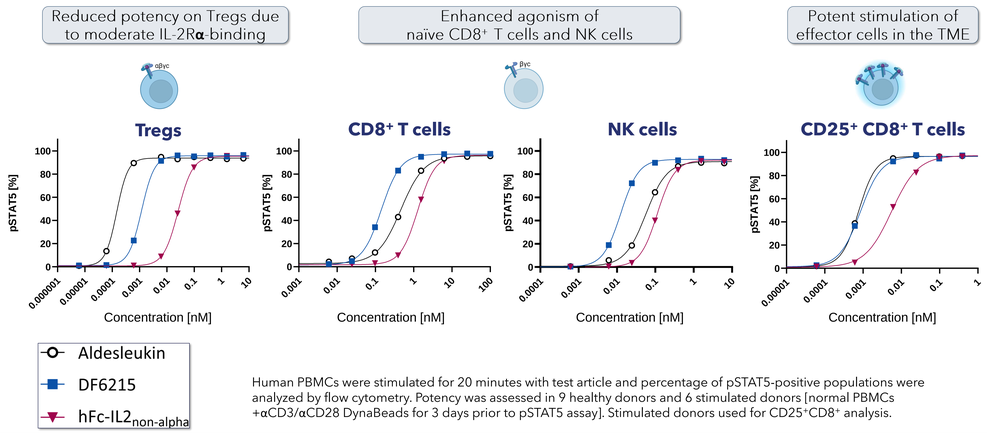
DF6215 has extended half-life and optimized IL-2Rα (CD25) binding



DF6215 improves human CD8⁺ T cell proliferation compared to a non-alpha tool molecule

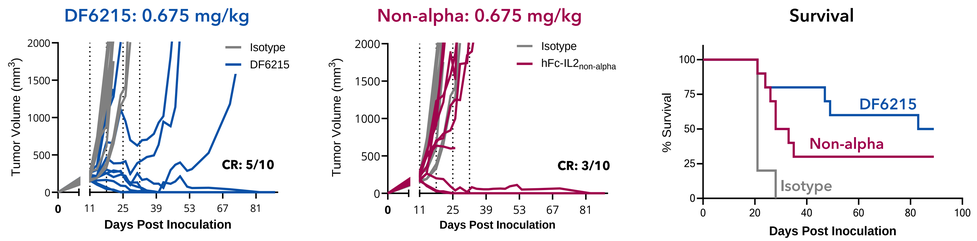


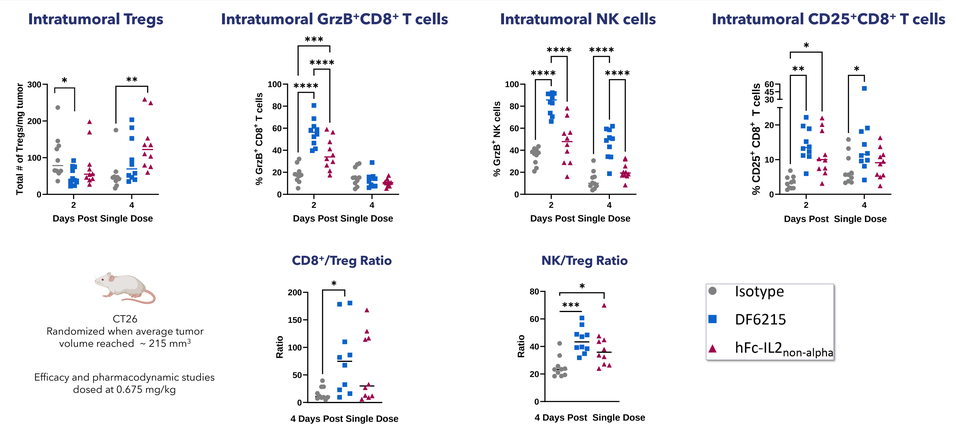
DF6215 exhibits increased potency on activated CD8⁺ T cells compared to a non-alpha IL-2 and reduced potency on T regulatory cells compared to aldesleukin



Human PBMCs were stimulated for 20 minutes with test article and percentage of pSTAT5-positive populations were analyzed by flow cytometry. Potency was assessed in 9 healthy donors and 6 stimulated donors [normal PBMCs +αCD3/αCD28 DynaBeads for 3 days prior to pSTAT5 assay]. Stimulated donors used for CD25⁺CD8⁺ analysis.

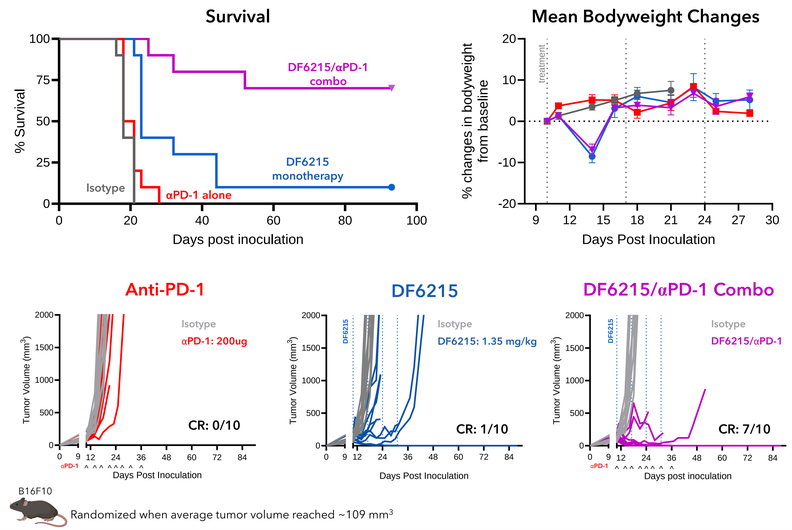
DF6215 drives greater therapeutic benefit than a non-alpha IL-2 in the CT26 mouse tumor model



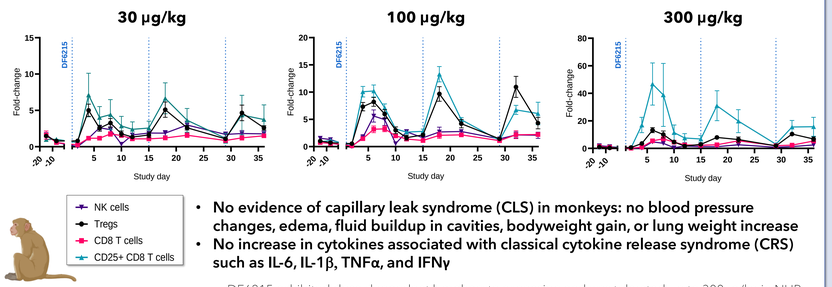


DF6215 enhances effector cells in the tumor microenvironment (TME) and increases effector-to-Treg ratio in the TME more than non-alpha IL-2

DF6215 synergizes with PD-1 blockade in the "cold" B16F10 melanoma tumor model without adding toxicity



DF6215 preferentially expands activated CD8⁺ T cells in the periphery of NHP without evidence of capillary leak syndrome or cytokine release syndrome



- No evidence of capillary leak syndrome (CLS) in monkeys: no blood pressure changes, edema, fluid buildup in cavities, bodyweight gain, or lung weight increase
- No increase in cytokines associated with classical cytokine release syndrome (CRS) such as IL-6, IL-1β, TNFα, and IFNγ

DF6215 exhibited dose dependent lymphocyte expansion and was tolerated up to 300µg/kg in NHP

DF6215 is an alpha-active IL-2 that potently and preferentially stimulates proliferation and activation of cytotoxic CD8⁺ T cells and NK cells and is better tolerated than aldesleukin

DF6215 was found to:

- Increase proliferation of immune cells and preferentially expand anti-tumor effector cells compared to non-alpha IL-2 molecules (maximizing the anti-tumor effector:Treg ratio)
- Increase granzyme B expression in tumor-infiltrating CD8⁺ T cells and NK cells
- Demonstrate effective therapeutic efficacy in mouse cancer models as a single agent as well as in combination with immune checkpoint blockade
- DF6215's extended half-life, tuned IL-2Rα binding and increased IL-2Rβγ agonism expand IL-2's therapeutic index.

DF6215 is currently being evaluated in a Phase 1/1b clinical trial in patients with advanced solid tumors (NCT06108479).