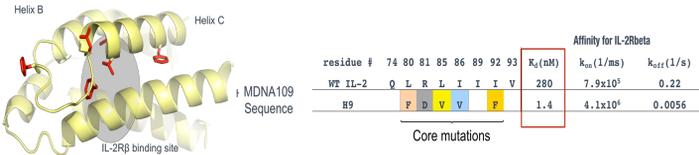


**MDNA109: An IL-2 Superkine™ Agonist  
For Cancer Immunotherapy**

**PROGRAM OVERVIEW**

- Medicenna is developing a pipeline of engineered cytokine products (Superkines and Empowered Cytokines), with pharmacologically-optimized receptor-binding properties.
- MDNA109 is an IL-2 cytokine variant with 200X greater affinity for the IL-2Rβ than native IL-2, that leads to preferential expansion of effector cells over regulatory T cells.
- MDNA109's receptor binding properties were engineered to maximize the anti-tumor effects mediated by IL-2, while reducing the mitigating immune effects and the potential for the severe side effects observed with Proleukin® (aldesleukin).

**MDNA109 is currently in preclinical development, with clinical development targeted for late 2018.**



**IL-2 Receptor Biology**

- IL-2 signals through binding to either *high affinity* or *intermediate affinity* receptor complexes on lymphocytes.
- High affinity receptor – a ternary complex of CD25, IL-2Rβ and IL-2Rγ – expressed on T<sub>reg</sub> cells.
- Intermediate affinity receptor – binary complex of IL-2Rβ and IL-2Rγ – expressed on naïve T cells.
- Binding of IL-2 to either receptor triggers downstream signalling through the JAK-STAT, MAP kinase, and PI3K pathways, leading to proliferative responses.
- Naïve T cells express only IL-2Rβ and IL-2Rγ and at low levels compared to activated and T<sub>reg</sub> cells, which express the high affinity receptor at higher levels, leading to relative insensitivity of this desired T cell population to expansion by exogenous IL-2.
- Additionally, CD25 expression on endothelial cells is implicated in the toxicity and vascular leak seen with treatment by Proleukin.

**Selective Targeting of Effector T cells**

- MDNA109 was designed by the lab of Chris Garcia at Stanford University to bind the intermediate affinity receptor with higher affinity than WT IL-2. Nature 2012 PMID 22446627
- Yeast display, selecting for muteins with enhanced IL-2Rβ binding affinity, followed by biophysical and functional characterization.
- MDNA109 selectively expands CD8+ T cells in vivo, has superior anti-tumor activity and does so with less evidence of adverse effects in mouse models.
- Combination therapy with anti PD-1 in mouse model produces robust curative response in a dose-dependent manner.

**IL-2 - A PROVEN CANCER IMMUNOTHERAPY**

- IL-2 plays a central role in the immune system, stimulating both the proliferation of effector T cells and regulatory T cells.
- Proleukin, a bacterially expressed wild-type IL-2 was approved by the FDA for the treatment of metastatic renal cell carcinoma and metastatic melanoma in 1992 and 1998 respectively.
- While yielding robust, durable responses in some patients, Proleukin's utility was limited by i) a minority of patients demonstrating clinical response and ii) a significant toxicity profile that required in-patient administration in specialist centers.

**MDNA109's engineered receptor binding properties is intended to overcome both these limitations**

