Medicenna is a clinical-stage immuno-oncology company advancing novel, highly selective Superkines for the treatment of a broad range of cancers. The company’s Superkines, licensed from Stanford University, are unique immune modulators that have been pharmacologically optimized for specific receptor-binding properties with the additional capacity to modulate signaling pathways (Fig. 1). Studies published in Nature and other prestigious journals have demonstrated the remarkable ability of Superkines to precisely and potently activate tumor-killing immune cells for cancer immunotherapy and alter the immunosuppressive tumor microenvironment (TME).

“Superkines have a very high affinity for specific receptor subtypes to either selectively activate tumor-killing immune cells or block immunosuppressive cells of the tumor microenvironment,” said Medicenna’s president and CEO Fahar Merchant. “By using these strategies alone or with existing immunotherapies, we may be able to develop sophisticated targeted treatment for cancers that badly need better options.”

Tailoring IL-2 to optimize T cell responses

IL-2 was one of the first effective immunotherapies developed to treat cancer owing to its proficiency at expanding T cells, the central players in cell-mediated immunity. The interleukin-2 receptor (IL-2R) is composed of three different subunits, IL-2Rα (CD25), IL-2Rβ (CD122) and IL-2Rγ (CD132). The complete receptor is usually found on regulatory T (Treg) cells, which dampen an ongoing immune response. By contrast, another receptor composed of only the IL-2Rβ and IL-2γ components is more often found on naive immune cells, which await instructions before seeking out cancer cells.

MDNA109 is an engineered version of IL-2 that binds up to 1,000 times more effectively to IL-2Rβ, thus greatly increasing its ability to activate and proliferate the immune cells needed to fight cancer. Because it preferentially binds to IL-2Rβ, MDNA109 drives the expansion and responses of effector T cells and Natural Killer (NK) cells over Treg cells.

Proleukin is a native IL-2 drug approved by the US Food and Drug Administration for the treatment of metastatic renal cell carcinoma and metastatic melanoma. Unfortunately, only a minority of patients demonstrate a clinical response to this drug, and its significant toxicity requires inpatient administration at specialist centers.

Compared with Proleukin and other IL-2 variants in development, MDNA109’s receptor-binding properties are engineered to maximize the antitumor effects mediated by IL-2, while reducing the mitigating immune effects and severe side effects observed with Proleukin. MDNA109 is the only IL-2 in development that selectively binds to CD122. MDNA109 has also been shown to effectively combat energy (exhaustion) of NK cells following the loss of major histocompatibility complex class I molecules, which occurs frequently after cancer immunotherapy. Unlike other next-generation IL-2 molecules in development, such as NKTR-214 (Nektar Therapeutics), MDNA109 specifically targets IL-2Rβ, resulting in much higher activation of effector T cells relative to Treg cells. Furthermore, long-acting versions of MDNA109 with tunable pharmacokinetics, generated by genetic fusion to Fc or albumin domains, have the potential to achieve extended half-life comparable to NKTR-214 with the convenience of subcutaneous administration. Finally, MDNA109 and its long-acting versions are relatively simple to manufacture and can be genetically fused to antibodies to create ImmunoCytokines or combined with other treatment modalities.

IL-4 and IL-13 Superkines: unblinding the tumor microenvironment

Both IL-4 and IL-13 participate in the survival and development of tumor-associated macrophages and myeloid-derived suppressor cells, which are key components of an immunosuppressive TME. Furthermore, overexpression of IL-4R occurs in 20 different cancers, affecting over a million patients each year.

MDNA132 is a modified IL-13 Superkine that is 16 million times more likely to bind to the decoy IL-13Rα2 subunit of the IL-13R complex. IL-13Rα2 is not normally expressed on healthy cells, but is highly expressed on some tumors, such as glioblastoma, breast cancer, colon cancer, and pancreatic cancer. MDNA132 is available to license for use as an attractively differentiated targeting domain for inclusion in chimeric antigen receptor (CAR)-T cell constructs.

Arming CAR-T cells and oncolytic viruses with Superkines

Arming CAR-T cells or oncolytic viruses with MDNA109 or MDNA132 Superkines can provide a cytokine boost to stimulate effector T cells or block the immunosuppressive TME. By fusing Superkines to toxic payloads, antibodies, or inactive protein scaffolds, Medicenna is able to generate Empowered Cytokines, ImmunoCytokines and long-acting Superkines, respectively, providing additional functionality, targeted delivery, and improved pharmacokinetics.

“The remarkable flexibility of the Superkine platform and its synergism with current immunotherapies has the unparalleled potential to transform the lives of patients with cancer,” said Merchant. “Medicenna is currently seeking additional partners to further our science, platform, and programs.”

**Fig. 1** | Superkines derived from libraries of diverse cytokines are optimized for specific, high-affinity binding with a range of signaling amplitudes for superior biological potency.

**MDNA132** is a modified IL-13 Superkine that is 16 million times more likely to bind to the decoy IL-13Rα2 subunit of the IL-13R complex. IL-13Rα2 is not normally expressed on healthy cells, but is highly expressed on some tumors, such as glioblastoma, breast cancer, colon cancer, and pancreatic cancer. MDNA132 is available to license for use as an attractively differentiated targeting domain for inclusion in chimeric antigen receptor (CAR)-T cell constructs.

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