MaveriX Oncology, Inc.
www.maverixoncology.com

Co-targeting cancer and TIME with conditionally activated small molecule therapeutics

MaveriX Oncology has developed the IMPACT-2X platform for the design of first-in-class small-molecule therapeutics—which are conditionally activated by highly expressed hydroxylases in cancer and the tumor immune microenvironment (TIME)—to treat multiple solid tumors.

Global biotechnology company MaveriX is focused on the development of conditionally activated small-molecule therapeutics designed to simultaneously kill cancer cells, reduce the immunosuppressive nature of the tumor immune microenvironment (TIME), and stimulate the immune system to attack tumors.

Its technology platform, IMPACT-2X, leverages hitherto unexploited insights into hydroxylase biology within the TIME. The resulting conditionally activated small-molecule drug conjugates (CA-SMDCs) selectively deliver their therapeutic payloads to tumor cells as well as to TIME-associated immunosuppressive cells (Fig. 1).

"At MaveriX, our goal is to revolutionize targeted cancer therapy with a new generation of conditionally activated therapeutics exhibiting potent anti-tumor activity with markedly reduced toxicity to normal tissue, and a widened therapeutic index," said Steven Everett, CEO of MaveriX.

MaveriX's two current lead programs—MVX484, and the corresponding solubilized prodrug MVX505—facilitate the oral and intravenous administration of a nucleoside (NUC)-based CA-SMDC-NUC, respectively. CA-SMDC-NUCs cause intra-tumoral DNA damage and cellular stress triggering an immunomodulatory and immunostimulatory response reflected in an exceptionally broad anti-tumor activity and safety profile providing mechanistic proof-of-concept. The IMPACT-2X is a multi-target, multi-asset platform technology with the potential to generate a deep pipeline of product candidates with single-agent activity with mechanistic synergy supporting combination chemo- and immunotherapy.

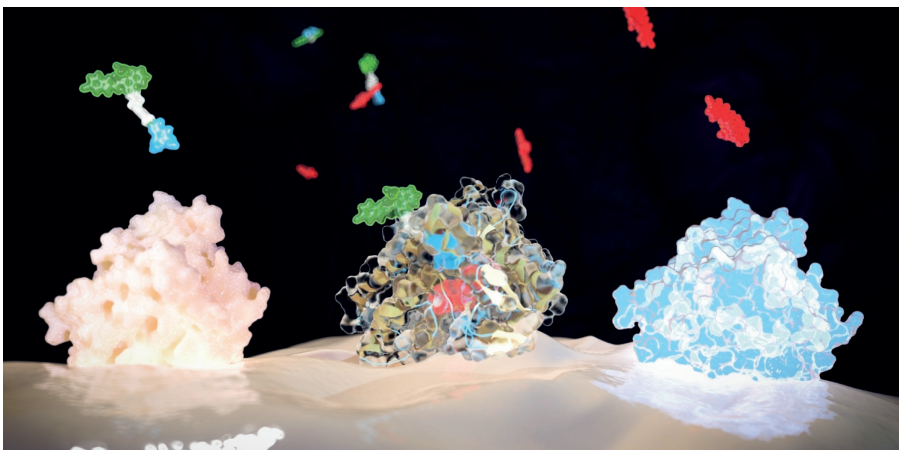

Fig. 1 | CA-SMDCs exploit tumor-associated hydroxylases. Inactive CA-SMDCs (green) exploit tumor-associated hydroxylases to selectively deliver active payloads (red) to cancer and the TIME. CA-SMDCs, small-molecule drug conjugates; TIME, tumor immune microenvironment.

A 'two-in-one' front against cancer

While immunotherapy has dramatically advanced our ability to fight cancer over the past decade, neutralizing the immunosuppressive nature of the TIME without compromising self-tolerance systemically continues to pose a substantial challenge for the wider implementation of immunotherapies. The main barrier to improving the response rates to immunotherapy remains the dearth of viable, tumor-specific targets.

MaveriX took a different tack: rather than focusing on finding novel, tumor-specific molecular targets, the company has identified metabolic targets that are co-expressed in both cancer and the TIME. Specific hydroxylases are expressed to a high frequency in most solid tumors and are practically undetectable in normal tissues. Furthermore, hydroxylases are targets for multiple well validated immunosuppressive metabolic pathways within the TIME associated with immunosuppressive cell subsets including regulatory T cells, cancer-associated fibroblasts, myeloid-derived suppressor cells, and tumor-associated macrophages. Hydroxylase deregulation and over-expression is a key hallmark of cancer due to metabolic reprogramming in cancer and associated metabolic crosstalk with the TIME.

Capitalizing on this TIME-specific hydroxylase activity, the team at MaveriX has developed its proprietary CA-SMDC platform, which consists of a drug or payload that is conjugated to a Pro-XACT 'molecular mask' by a hydroxylase cleavable linker. Once the systemically stable and inactive CA-SMDC has honed into the TIME, it releases its active payload directly into the cells expressing tumor-associated hydroxylase, causing both direct killing of tumor cells and the eradication of immunosuppressive cells. The net result is an 'immunogenically hot' tumor that is highly susceptible to further immune attack. Furthermore, CA-SMDC payloads can be tailored for single-agent activity in the clinic while stimulating innate and adaptive immune attack on tumors by natural killer cells and cytotoxic T cells, respectively.

"The exploitation of hydroxylases in cancer biology and tumor immunosuppression paired with conditionally activated small-molecule therapeutics is a potentially disruptive approach to targeted cancer therapy," said Everett. "There are obvious advantages over conditionally activated biologic antibodies and antibody drug conjugate technologies, primarily relating to tumor selectivity, solid tumor penetration, and oral administration in the clinic."

Multiple development candidates

MaveriX has several targeted and immuno-oncology CA-SMDC-based programs focused on the development of multiple drug candidates addressing different solid tumors with clear clinical unmet need. The company's lead program is completing formal IND-enabling studies targeting clinical entry in the first half of 2023. This program includes a solid tumor phase 1a dose-escalation with disease-specific expansion arms followed by a phase 1b combination chemotherapy and immunotherapy.

"We are actively seeking to identify industry and clinical partners to advance our programs to clinical proof-of-concept and to expand our overall platform and pipeline," said Everett. "MaveriX is poised to maximize the impact of its unique platform to bring new and improved treatment options to patients that suffer from cancer."

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