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Improving CAR-T cell therapy by using a successful mode of action in a new field

Priothera's immunomodulator mocravimod is an adjunctive and maintenance therapy for acute myeloid leukemia and is poised to enter a pivotal trial. It is now also being developed to unleash the full power of CAR-T therapy.

The advent of chimeric antigen receptor T cell (CAR-T) therapy as a novel form of immunotherapy made it possible to treat cancers for which few treatment options existed, especially hematological malignancies. Its success is reflected in the increasing number of CAR-T approvals in new indications. Yet despite some great successes, CAR-T therapies are often beset by severe side effects, including cytokine release syndrome (CRS) and neurotoxicity, and they often have limited efficacy in many patients, e.g. approx 60% of CAR-T treated patients are relapsing. Nevertheless, CAR-T therapy remains a key and last resort treatment for patients with advanced cancers who have not responded to previous therapies.

Priothera is striving to change the fortunes of CAR-T therapies, and the patients who could benefit from them, by combining a CAR-T approach with the small-molecule immunomodulator mocravimod, which has the potential to not only reduce the side effects associated with CAR-T, but even more important, also improve its efficacy.

Mocravimod is currently in late-stage development for use in conjunction with allogenic hematopoietic stem cell transplantation (HSCT) to treat acute myeloid leukemia (AML), which is not presently amenable to CAR-T. For many intermediate and high-risk AML patients, as well as those with other hematological malignancies, chemotherapy followed by HSCT is the only potentially curative treatment option. However, HSCT, like CAR-T, often produces significant side effects, specifically graft-versus-host disease (GvHD), which can be fatal. To manage GvHD, clinicians administer immunosuppressants that in turn supress the antitumor response generated by HSCT, creating a therapeutic catch-22 situation.

Mocravimod has recently received US Food and Drug Administration (FDA) investigational new drug (IND) and European Medicines Agency (EMA) clinical trial application (CTA) approvals. The FDA and EMA have designated mocravimod an orphan drug, and the FDA gave it fast-track status. The company is set to begin a global, pivotal phase 2/3 trial with mocravimod in AML patients undergoing allogenic HSCT.

This novel, synthetic agonist of sphingosine 1-phosphate receptors (S1PR) has a crucial role in lymphocyte trafficking from lymphoid tissues, such as bone marrow and lymph nodes, to peripheral blood and tissues. Delivered as a prodrug during and after HSCT, mocravimod blocks the migration of alloreactive T cells out of lymphoid tissues and consequently reduces GvHD (Fig. 1). This mode of action is being successfully used in auto-immune indications to keep auto-reactive T cells in check, such as in multiple sclerosis, but it is yet to be applied to oncohematology settings.

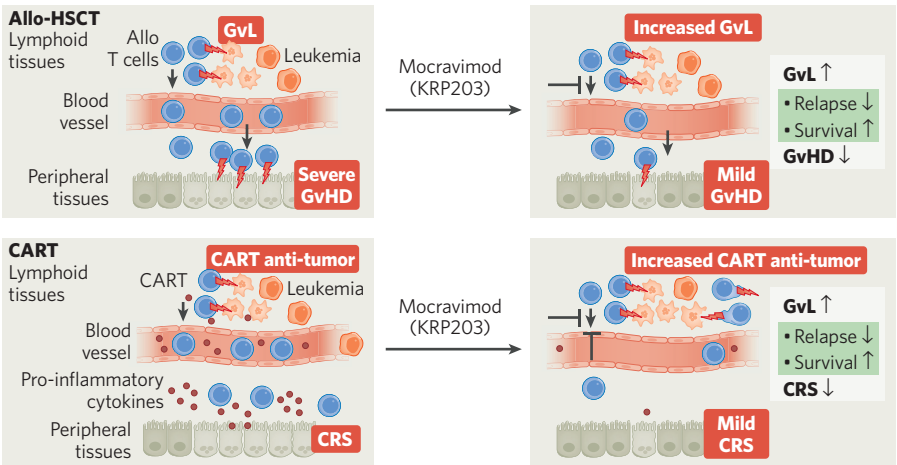

Fig. 1 | Mocravimod boosts the efficacy of CAR-T therapy. Using the same mechanism of action previously described for HSCT (top), mocravimod blocks CAR-T cells from exiting lymphoid tissue where malignant hematological cells reside. This enhances the efficacy of CAR-T, and stops CAR-T cells entering peripheral tissues—where they can cause cytokine release syndrome (CRS)—and the CNS, where they might have neurotoxic effects. CAR-T, chimeric antigen receptor T cell; GvHD, graft-versus-host disease; GvL, graft-versus-leukemia; HSCT, hematopoietic stem cell transplantation.

By sequestering these alloreactive T cells within the lymphoid tissue, mocravimod, which is not an immunosuppressant, promotes a graft-versus-leukemia (GvL) response within the lymphoid tissues where the malignant hematological cells reside. At the same time, these alloreactive T cells are unable to migrate to other parts of the body where they might promote GvHD. In this way, mocravimod simultaneously enhances the benefits of allogenic HSCT and mitigates the downsides effects. This concept has been demonstrated in preclinical and clinical studies, supporting the imminent start of a pivotal trial of mocravimod in AML patients receiving allogenic HCST.

The same logic applies to using mocravimod as an adjunctive treatment for CAR-T therapy (Fig. 1). By sequestering CAR-T cells in bone marrow and lymphoid tissues, they become more effective at destroying the malignant hematological cells they encounter within the lymphoid tissue. Just as the retention of T cells within lymphoid tissue reduces GvHD in allogenic HSCT, mocravimod should reduce CRS, as well as the less-understood neurotoxicity associated with CAR-T therapy (which may result from CRS and/or T cell migration to the central nervous system (CNS)).

Previous research has shown that the disappearance of CAR-T cells from the bone marrow correlates with tumor relapse in cancer patients. Priothera's preclinical studies have demonstrated that mocravimod leads to the retention of CAR-T cells within the bone marrow and lymph nodes, enhancing their activation and antitumor efficacy. The same CAR-T-cell-sequestering effect of mocravimod was shown to reduce peripheral cytokine levels following CAR-T. And, in addition to preventing CAR-T cells migrating to the CNS, where they can cause neurotoxicity, mocravimod might also decrease CAR-T related CNS toxicity.

Priothera is continuing its preclinical CAR-T investigations, to assess the efficacy, durability of CAR-T cells responses and establishment of solid CAR-T cell memory; and whether mocravimod prevents cytokine-mediated damage and protects the CNS from unwanted CAR-T effects.

By building on the encouraging results already obtained with mocravimod in HSCT, Priothera has de-risked mocravimod in CAR-T and maximized the chance of success in this crucial immunotherapy.

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