Carisma Therapeutics is developing unique CAR macrophage therapies to treat solid tumors. The company’s lead CAR-M program, CT-0508, is ready to enter phase 1 testing.

Carisma Therapeutics is developing a unique, differentiated immuno-oncology (IO) treatment for solid tumors based on chimeric antigen receptor macrophages (CAR-M). Current IO treatments have offered improved outcomes for some cancer patients but leave behind many non-responders. In tumors that are ‘cold’ and lack infiltrating T cells, for example, checkpoint inhibitors tend to be ineffective. CAR-T cells, engineered to recognize tumor-specific antigens, although successful in some blood cancers and lymphomas, have not been effective in solid tumors to date. To overcome these hurdles, Carisma has developed CAR-M, leveraging the natural role of macrophages to initiate a multi-faceted innate and adaptive anti-tumor response. The company’s lead CAR-M program, CT-0508, will soon enter phase I testing, having shown increased overall survival in a preclinical model of HER2+ cancer.

Carisma’s CAR-M therapies rest on a breakthrough platform technology that enables genetic manipulation of primary macrophages ex vivo and re-introduction into patients, enabling multiple therapeutic applications in and beyond oncology. CAR-M is an individualized therapy that begins with isolation of primary monocytes from blood drawn from a patient. The cells are then transduced with the desired antigen-specific chimeric receptor, for example, anti-HER2, using proprietary viral or nonviral methods. The resulting CAR-M cells are cryopreserved and shipped back to the patient for reinfusion. Reinfused CAR-M are actively recruited to tumor sites, with ~30% accumulating in tumors within 5 days in preclinical models. Like a Trojan horse, CAR-M may be able to reach immunologically ‘cold’ tumors.

Once in the tumor, CAR-M are activated by tumor-associated antigen engagement with the CAR, signaling via CD3-ζ to phagocytose the tumor cell and release cytokines and chemokines that ‘warm up’ the tumor microenvironment (TME). Virally transduced CAR-M are locked into a pro-inflammatory M1 phenotype during the manufacturing process. They produce locally acting mediators that repro-gram the TME, drawing in T and natural killer (NK) cells, activating nearby antigen presenting cells (APCs), notably dendritic cells (DCs), and repolarizing tumor-associated macrophages (TAMs) toward an M1 phenotype. In addition to direct phagocytosis of tumor cells, CAR-M present a patient’s unique array of neoantigens to T cells, leading to a broad adaptive immune response that has the potential to generate long-term immunity beyond the antigen targeted by the CAR (Fig. 1).

**Promising lead candidate**

Based on impressive preclinical results, Carisma’s lead candidate CAR-M therapy targeting HER2+ cancers, CT-0508, is being rapidly advanced to the clinic, with investigational new drug (IND) approval by the US Food and Drug Administration and phase 1 start targeted for late 2020. HER2-specific CAR-M were tested in two xenograft models. In immuno-deficient mice injected with HER2+ ovarian cancer (SKOV3) cells, a single HER2-specific CAR-M injection improved overall survival, with 50% of treated mice surviving to day 100 compared with loss of all control animals to cancer by day 60. In immunocompetent mice injected with CT26 HER2+ tumor cells, CAR-M shrunk HER2+ tumors with a 75% complete response rate and also showed activity against a contralateral HER2- tumor, indicating epitope spreading via T cell activation.

While targeted HER2+ cancer drugs have led to improved survival in breast and gastric or gastro-esophageal junction cancers, there remains unmet need in advanced HER2+ cancers, where efficacy is lower and fewer agents are approved; as well as in diverse HER2+ cancers (for example, metastatic lung, ovarian, colon and bladder cancers), for which there are no approved targeted agents. HER2 has several advantages as a target antigen for CAR-M. In addition to being expressed in a variety of solid tumor types with a significant medical need, HER2 is not shed or internalized and is only expressed at low levels in non-tumor tissues. Because HER2 expression is typically maintained over the course of disease, CT-0508 is expected to be effective against metastatic disease, for example, in liver and lung, as well as primary tumors.

In addition to establishing the safety of the vector-transduced CAR-M cells administered intravenously, the phase 1 study will incorporate readouts to validate all aspects of CAR-M’s proposed mechanism of action, including trafficking to tumor (assessed via PET imaging and post treatment biopsies), tumor phagocytosis, expression of multiple cytokines and chemokines and cell recruitment, conversion of TAMs to a pro-inflammatory M1 state, and epitope spreading via T cell activation.

**Partnering for progress**

In anticipation of the phase 1 trial, good manufacturing practice (GMP) cell product manufacturing methods and partnerships have been put in place for all components, including Oxford Genetics for plasmid production, Wuxi for vector assembly and Miltenyi for primary cell manufacturing. Carisma is actively seeking additional alliances to support late-stage clinical and commercial activities in oncology, including two additional programs in mesothelin- and prostate-specific membrane antigen (PSMA)-positive cancers, and other undisclosed oncology targets. Further partnerships are envisioned to extend CAR-M therapy to additional therapeutic areas: in neurodegenerative disease, such as Alzheimer disease and Parkinson disease, CAR-M are being developed to specifically target and clear aggregated pathogenic proteins. Similarly, CAR-M engineered via nonviral methods can be directed to develop an M2, immunosuppressant phenotype that holds promise for multiple diseases characterized by inflammation and fibrosis.

**Fig. 1** The unique mechanism of action of chimeric antigen receptor macrophage (CAR-M) therapies. MHC, major histocompatibility complex.