CAR-M Industry Landscape Analysis: Chimeric Antigen Receptor-Macrophage (CAR-M) Stakeholders, Technologies, Pipeline, Partnering and Financing

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La Merie Publishing
Carrer Núria, 10, 3, 2a
E-17500 Ripoll
info@lamerie.com

Table 3b: Product Partnering of CAR-M Companies

Myeloid Therapeutics:

Partner (Source)	Subject	Rights	Economic Terms
Prime Medicine (PR Mar 31, 2022)	To further develop Myeloid's RNA-based, retrotransposon mediated gene-insertion technology, (RetroT™)	Exclusive option to gain control of the intellectual property estate	$45 mln up-front; milestone & option exercise payments, sales-based royalties

Shoreline Biosciences:

Partner (Source)	Subject	Rights	Economic Terms
Kite, a Gilead company (PR June 17, 2021)	Expertise in iPSC differentiation and genetic reprogramming used for cell therapies	Initial focus on CAR NK cells; option to expand collaboration to include an iPSC CAR macrophage program	Not disclosed upfront payment; up to $ 2.3 bln milestone payments, royalties

"Off-the-shelf" induced pluripotent stem cell- (iPSC) derived Chimeric Antigen Receptor Macrophages (CAR-iMAC) for cancer immunotherapy are the subject of the strategic collaboration of CellOrigin Biotech and Qilu Pharma. Economic terms of the development, manufacturing and commercialization agreement were not disclosed.

Myeloid Therapeutics' collaboration with Prime Medicine aims at further developing Myeloid's RNA-based gene insertion technology RetroT for which Prime Medicine will have an exclusive option to gain control of the intellectual property (IP) estate. The amount of the US$ 45 mln up-front payment is identical to that which received Carisma Therapeutics from Moderna Therapeutics.

While the up-front payment of Kite to Shoreline Biosciences was not disclosed, the overall value of the deal might reach US$ 2.3 bln if all milestones will be met. Kite's basic interest lies in iPSC-derived cells, primarily in iPSC-CAR-NK cells with an option to include an iPSC-CAR-M program.

Apart from the agreements listed in Table 3, three of the CAR-M companies also have entered into product, manufacturing and technology-based collaboration and/or licensing agreements

Monocyte cellular therapy intended to treat solid tumors that overexpress human epidermal growth factor receptor 2 (HER2) metastasis. CT-0525 is in pre-clinical development.

Carisma is developing **CT-1119**, an ex vivo gene-modified autologous CAR-Macrophage cellular therapy to target mesothelin-positive solid tumors. CT-1119 is in pre-clinical development. Preclinical data demonstrate that CT-1119 can mediate phagocytosis, tumor cell killing, and pro-inflammatory cytokine release and control tumor growth in pre-clinical lung cancer models. This data demonstrates that CAR-M may be a feasible and differentiated approach that could be tested in the treatment of mesothelin expressing solid tumors such as lung cancer, mesothelioma, ovarian cancer, pancreatic cancer, and other solid tumors.

Carisma is also developing **CT-0729**, an ex vivo gene-modified autologous CAR-Macrophage cellular therapy to target prostate-specific membrane antigen for treatment of metastatic castration-resistant prostate cancer. CT-0729 is in discovery.
Carisma has partnered with Moderna Therapeutics to develop the next generation of macrophage-targeted in-vivo therapies to address multiple cancer targets.

5.2 CellOrigin Biotech

CellOrigin Biotech is located in Hangzhou, China. In addition to the company's scientific co-founder Jin Zhang, trained at Harvard Medical School, experienced leaders from Zheijang University and top pharmaceutical and biotech companies founded CellOrigin Biotech in the year 2018. CellOrigin Biotech is dedicated to the development of genetically engineered pluripotent stem cell (iPSC)- derived immune cell therapies (such as macrophages, NK cells).

Financing

CellOrigin Biotech raised until March of 2022 US$ 15.7 mln from five investors including EFung Capital and Jifeng Ventures. In March 2022, the company secured a new round of investment of about 100 million RMB (about US$ 14.4 mln) from Jifeng Ventures, Kunlun Capital, Yinxinggu Capital and Efung Capital (BioSpectrum Asia March 30, 2022). Kunlun Capital, Shulan Health and Nest.Bio Ventures participated in previous investment rounds (Press Release Oct 15, 2021).

further stimulate an anti-tumor immune response through the secretion of pro-inflammatory cytokines and the presentation of tumor-associated antigens.

Shoreline Bioscience's iPSC Macrophage technology is based on work conducted at the company's scientific co-founder Dan Kaufman at UC San Diego. Pouyanfard et al. (2021) demonstrated the efficient derivation of macrophages from human induced pluripotent stem cells (iPSCs). These macrophages have phenotypic and genotypic characteristics similar to monocytes/macrophages isolated from human peripheral blood. They also demonstrate the ability to polarize these iPSC-derived macrophages (iPSC-Macs) to M1 and M2 populations. Specifically, M1 iPSC-Macs have pro-inflammatory characteristics including expression of CD40 and CD80 on the cell surface, produce increased amounts of TNF-a and IL-6 detected in the supernatant, as well have increased expression of inflammatory cytokines/chemokines (TNF-a, IL-6, IL-1b, IL-12, CCL2, CCL3 and TRAIL) and increased expression of matrix metalloproteases (MMPs).

Macrophages engineered with CAR constructs have been gaining interest for cancer immunotherapy, because macrophages are capable of infiltrating into tumor microenvironment, detecting phagocytic targets and engulfing them, as well as stimulating other endogenous immune cells. Kong et al. (2022) from the Kaufman group successfully generated CAR-expressing induced pluripotent stem cells (iPSCs) through either PiggyBac transposon-mediated transfection or lentiviral transduction. Subsequently, the CAR-expressing iPSCs were differentiated into macrophages (**iPSC-CARMACs**). The CAR expression in undifferentiated iPSCs were high and stable, but gradually downregulated during the differentiation into macrophages. Due to the loss of CAR expression, these iPSC-CARMACs only modestly improved phagocytic activity compared to wild-type iPSC-derived macrophages (iPSC-MACs) *in vitro*. Additionally, they did not find a significant benefit for *in vivo* anti-tumor activity of the iPSC-CARMACs compared to iPSC-MACs.

They hypothesized the deficiency of anti-tumor activity might be due to the loss of CAR-expression that can become silenced after random integration into the genome. Therefore, to test this hypothesis as well as improve and stabilize the CAR expression, they engineered human iPSCs using CRISPR-Cas9 mediated CAR insertion into AAVS1 locus, a known safe harbor locus that is less prone to genetic silencing. They engineered a series of CAR constructs containing the same anti-Mesothelin (Meso) extracellular single-chain antibody variable

7.6 MT-301

Myeloid Therapeutics is reprogramming circulating and tumor associated myeloid cells to activate their ability to elicit anti-tumor adaptive immunity by phagocytosis, cytokine secretion and antigen presentation is an attractive approach to harness and orchestrate systemic anti-tumor immunity. The company developed a novel **in vivo** myeloid cell engineering platform: Fcα Receptor (FcαR) fusion proteins. Unlike other chimeric antigen receptors (CARs) the construct was engineered by fusing a tumor recognition scFv with the alpha chain of human Fc receptors (CD89). The stable expression and function of these receptors requires endogenously expressed Fc receptor gamma chain, a protein with limited expression to immune cells, mostly myeloid cells.

Wang et al. (2022) presented that intravenous infusion of lipid-nanoparticle (LNP) encapsulating the Fca Receptor Fusion Construct mRNA results in the uptake of the LNP and expression of the chimeric receptor fusion protein by myeloid cells. In immunodeficient xenograft models of hepatocellular carcinoma, delivery of LNP mRNA encoding GPC3 targeted Fcα receptor fusion proteins (MT-301) resulted in anti-tumor efficacy, confirming the ability of this approach to program myeloid cells. This treatment was also associated with the initiation of broad systemic immune responses, characterized by tumoral accumulation of activated CD8+ T cells, reduced tumor associated Tregs and activation of antigen presenting cells in spleen.

MT-301 is currently in IND-enabling studies.

7.7 MT-302

Myeloid Therapeutics' novel class of chimeric antigen receptors (CARs) are known as **ATAK™** ("**A**ctivate, **T**arget, **A**ttack & **K**ill) Receptors. Myeloid's novel in vivo engineering platform specifically targets and activates myeloid cells to elicit broader anti-tumor adaptive immunity. Through this approach, Myeloid demonstrates that delivery of lipid-nanoparticles (LNPs) encapsulating mRNA results in selective uptake and expression by myeloid cells in vivo, leading to potent tumor killing in multiple cold tumor models. Myeloid's adaptations of mRNA for the myeloid compartment have enabled the evolution to deliver these receptors directly to the patient without any ex-vivo cell engineering.