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Redirecting innate cells to kill cancer

Immuno-oncology company Affimed is harnessing the power of innate immunity, with the help of its ROCK (Redirected Optimized Cell Killing) platform to change the lives of patients with cancer

Affimed is leading efforts to engage natural killer (NK) cells and macrophages to kill cancer cells. Having translated antibody engineering capabilities into clinical-phase candidates, Affimed has industry-leading assets and a platform primed to generate novel molecules, allowing it to further deepen its pipeline and creating partnering opportunities. With its validated platform, Affimed is the most advanced company in the field, which has enabled deals with Merck and Roche's Genentech.

Innate cells have emerged as a focal point of immunotherapy on the strength of their potential to enable potent antitumor immune attacks. These cells directly attack tumors while activating T and B cells to trigger an escalating immune response. In doing so, innate cells lead stronger, more targeted and, by extension, safer attacks.

Such thinking fueled the creation of multiple companies based on platforms designed to yield drugs that harness innate cells. Affimed stands out among the companies targeting innate immunity because of the advantages of its platform and the advanced nature of its pipeline, which is spearheaded by a drug in a registration-directed study.

> **Affimed has cleared the investigational new drug (IND) stage and is now initiating a clinical trial of AFM24 in patients with tumors known to express EGFR**

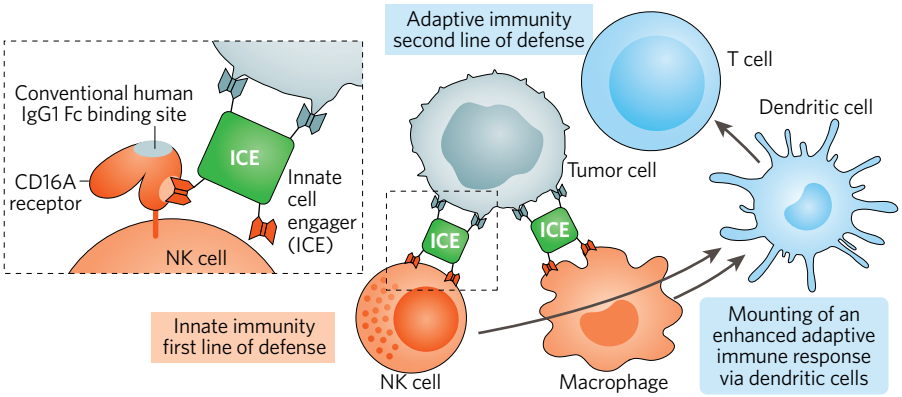

Fig.1 | Affimed's innate cell engagers (ICEs). Assets generated by the ROCK platform engage the CD16A receptor found on NK cells and macrophages at a particular epitope that is differentiated from the binding site of monoclonal antibodies.

Generating innate cell engagers

Affimed's pipeline is based on its ROCK platform, which it uses to engineer and screen multivalent antibodies with modular architecture. Affimed can customize innate cell engagers (ICEs) to different tumor targets through adjustable affinities and avidities, variable pharmacokinetic profiles and multi-specific targeting.

Assets generated by the platform engage the CD16A receptor found on NK cells and macrophages at an epitope which is differentiated from the binding site of monoclonal antibodies. The result is tetravalent bispecifics with high-affinity binding to CD16A that are free from interference by circulating polyclonal antibodies and are equally effective across all allelic variants (Fig. 1).

Those characteristics set ICE apart. Conventional and Fc-enhanced IgG antibodies lack the selectivity, effectiveness in low-affinity allelic variants and potency in low-density targets of ICEs. In contrast, other NK cell engagers in development are unable to activate macrophages, need co-activation signals or are prone to mediate fratricide of immune cells. Affimed's confidence in the advantages of the platform is based on clinical and preclinical data.

Validating the technology

Affimed's work to validate its technology is led by two assets. The furthest advanced of the assets is AFM13, an ICE designed for use in $CD30^+$ lymphomas. By engaging CD16A on immune cells and CD30 on cancer cells, AFM13 has yielded partial and complete responses as a monotherapy. In combination trials with a checkpoint inhibitor, a compelling overall response rate of 88% and an >40% complete response rate were achieved.

AFM13 has validated the potential of ICE in hematological cancers. Encouraged by the monotherapy data in T cell lymphoma, Affimed has begun a registration-directed study of AFM13 in patients with relapsed or refractory peripheral T cell lymphoma. The trial positions Affimed to realize a near-term revenue opportunity while working to bring AFM13 to larger patient populations, such as those with cutaneous T cell, B cell and Hodgkin lymphomas.

With AFM24, Affimed is looking to show that its engagers work in solid tumors. AFM24 engages epidermal growth factor receptor (EGFR), a receptor that is overexpressed in tumors, including colorectal cancer, non-small-cell lung cancer and triple-negative breast cancer. Monoclonal antibodies against the target already exist but are hamstrung by side effects and the impact of mutations on EGFR signal transduction.

By engaging NK cells and macrophages, AFM24 is designed to activate a broad antitumor immune response that overcomes resistance encountered by other drugs without causing safety issues. Affimed has generated preclinical data suggesting that AFM24 has those desired characteristics.

AFM24 has demonstrated potent killing across cell lines of different target densities and *KRAS/BRAF* mutations. Other tests linked AFM24 to lower inhibition of EGFR phosphorylation than approved EGFR drug cetuximab, suggesting that the ICE may be more tolerable.

A vast pipeline of opportunities

Affimed has cleared the investigational new drug (IND) stage and is now initiating a clinical trial of AFM24 in patients with tumors known to express EGFR, putting it on a path that could lead to approvals in multiple underserved populations. AFM24 is advancing in parallel with AFM13, which is closing in on an interim analysis of its registration-directed study and the initiation of other trials.

The clinical-phase assets are the tip of a vast pipeline of opportunities enabled by the ROCK platform. Affimed has further preclinical programs (AFM26, AFM28 and AFM32) and the ability to create new ICEs using the modular ROCK platform, equipping it to partner from drug discovery through to late-phase development. Affimed is seeking commercial and development partners for the lead clinical-phase assets and is exploring partnerships to accelerate and expand preclinical development.

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