

Programmable T cell engagers – a novel platform for logic-gated antibodies

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Medical need

Bi-specific T-cell engagers (BiTEs) such as blinatumomab have been successfully introduced in the last decade for the treatment of otherwise treatment-resistant acute lymphoblastic leukemia. BiTEs carry two different antibodies on their surface. This allows them to associate T cells with malignant B cells, triggering an immune response that kills the tumor cell. However, their (only relatively) safe and effective use is limited to hematologic malignancies. Solid tumors have a large number of antigenic epitopes on their surface, many of which are also present on healthy cells. T cell engagers therefore run the risk of not only destroying tumor cells. They are likely to overstimulate the immune system, causing severe side effects that may lead to discontinuation of therapy. Molecular scaffolds carrying multiple tumor-specific antibodies are needed. However, protein scaffolds have too many structural limitations to serve this purpose.

Suggested Solution

DNA is a better construction material than proteins. DNA origami has emerged as a powerful innovation in nanotechnology, allowing DNA building blocks to be assembled at will, almost like Lego bricks. Wagenbauer and his company, a spin-off of the Technical University of Munich, have created a DNA origami chassis to use as a nanoswitch for antibodies. This chassis carries tumor-targeting antibodies on its surface. Binding to a tumor-specific antigen pattern changes the conformation of this chassis in such a way that it switches open to present an antibody against a T-cell epitope, e.g., anti-CD-3. As a result, T cells are recruited to kill the tumor cell. Healthy cells are not affected by this switch; only when they specifically bind to a tumor cell are T cells activated. Because of this if-then logic, Plectonic named its invention a LOGic-gated antiBODY (LOGIBODY).

Translational Gap (ForTra Funding)

ForTra supported the technology transfer of LOGIBODY project between 2022 and 2023, ultimately enabling Wagenbauer's academic research team at TUM to start their own company.

Current Status/Perspective

Plectonic Biotech has demonstrated the proof of concept of specific T-cell engagement in vitro and validated the functionality of its technology in leukemia models in vivo. As LOGIBODY is a platform technology that allows for the exchange of antibodies in a modular fashion, the team is striving to extend the approach to solid tumors and hopes to realize a disruptive approach in cancer immunotherapy.

Reference

Wagenbauer KF et al. Programmable multispecific DNA-origami-based T-cell engagers. Nat Nanotechnol. 2023 Nov; 18 (11): 1319-1326. <http://doi.org/10.1038/s41565-023-01471-7>. Epub 2023 Aug 17.

Link to further information

<https://www.plectonic.com>