Using CAR T cells for treating cancer

After some spectacular successes in the treatment of advanced blood cancers, CAR T-cell immunotherapy has become a major beacon of hope in oncology. The first CAR T-cell therapies have received regulatory approval. Despite their success, these immunotherapies can have life-threatening side effects. A company called AVA Lifescience develops antibodies with high tumour specificity to use as the basis for effective precision-guided CAR T-cell therapies that are better tolerated by patients.

Binding of a CD19-specific CAR T cell to a leukaemia cell in a mouse model. Enlargement: CD19-CAR. Schematic drawing based on Michel Sadelain et al. (2003)
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Acute lymphoblastic leukaemia (ALL) is the most common blood cancer in children. In the majority of cases, ALL originates in B lymphocytes or their immature precursors. Nowadays, ALL can be treated effectively when detected at an early stage. However, in 10 to 15 percent of cases, ALL is resistant to chemotherapy and leads to relapses.

In May 2012 at the Children's Hospital of Philadelphia, USA, seven-year-old Emily Whitehead, an ALL patient, underwent CD19 CAR T-cell therapy, an immunotherapy that until then had only been tested in animals. She had been diagnosed with ALL in 2010 and had since undergone standard ALL treatment. However, after she suffered two severe relapses, the doctors had no other established therapy options available. Bone marrow transplantation was no longer an option either. Today, seven years after CAR T-cell therapy, Emily is still cancer-free and leads the life of a normal teenager.

The same approach has also led to cancer remission in patients with B-cell tumours who expected zero chance of remission. The successful treatment outcome has attracted worldwide attention and led to several hundred clinical studies and research projects. Two immunotherapies involving genetically engineered CAR T cells have since received US and European approval for treating certain advanced blood cancers. In September 2018, Heidelberg University Hospital was the first institution in Germany to be certified to use the new preparations for approved indications. Prof. Dr. Michael Schmitt, head of Cellular Immunotherapy / GMP Core Facility in Heidelberg, said: "In future, we expect to be able to use these immunotherapies for treating a number of other immune system cancers."

How CAR T-cell therapy works

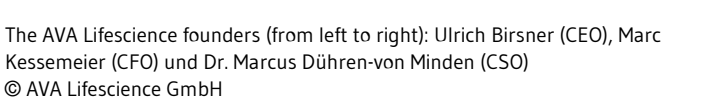
During carcinogenesis, cells that have tumour-associated antigens to which the body's immune system responds, change so that the tumour becomes invisible to the immune cells. CAR T-cell immunotherapy is a novel cell therapy approach in which patient-specific T cells (T lymphocytes that carry out adaptive immune responses) are equipped with an artificial receptor molecule by way of gene transfer. This receptor molecule is a so-called "chimeric antigen receptor" (CAR), which is able to recognise tumour antigens.

The T cells are obtained from the patient's blood using a method known as leukapheresis (similar to dialysis) and subsequently genetically modified in the laboratory. The CAR gene is stably integrated into the T-cell genome, for example by means of a viral vector, and can be passed on to the daughter cells as the T cells divide. The receptor itself is composed of an antigen binding domain (usually, as in the aforementioned cases, CD19, a B-lymphocyte antigen), a transmembrane domain (which is responsible for anchoring CAR onto the surface of the T cell), and an intracellular signalling domain (which, when CAR binds to the tumour cell, triggers a signalling cascade that activates the T cell). The T cells, which have been engineered to express the antigen-specific CAR, are expanded in the laboratory and returned to the patient via infusion. When a CAR T cell encounters a cell with the appropriate antigen, for example a CD19+ lymphoma cell, it binds to it and is activated, producing cytokines that kill the bound tumour cell and starts to divide.

It is difficult to imagine a better mode of action: even though only very few infused CAR T cells encounter a tumour cell, proliferation, which is associated with activation, increases their therapeutic efficacy whenever they do encounter one. In

addition, CAR T cells can remain in the body after the remission of the tumour and become active again when the tumour recurs.

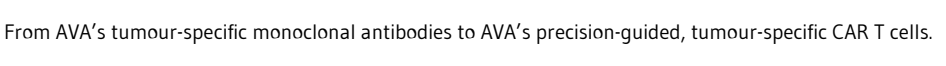
Problems and side effects



The AVA Lifescience founders (from left to right): Ulrich Birsner (CEO), Marc Kessemeier (CFO) und Dr. Marcus Dühren-von Minden (CSO)
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The new therapy, which uses the body's own T cells to fight cancer, is by no means ideal. First, it is extremely expensive. A single treatment with the Kymriah CD19 CAR T-cell gene therapy product sold by Novartis in Germany costs 380,000 euros (Source: Wikipedia). The therapy is also extremely stressful for patients. Prior to infusion with CAR T cells, the patient needs to be "conditioned" in the same way as patients receiving stem cell transplants. This means that body cells carrying the CAR target antigen need to be eliminated as much as possible using whole body irradiation and chemotherapy. As far as the CD19 antigen is concerned, this affects B-cell tumour cells as well as all B lymphocytes and thus the entire antigen-producing part of the immune system. In ALL and fast-growing B-cell lymphomas in particular, the rapid therapy-associated remission of the tumours can lead to tumour lysis syndrome, a metabolic imbalance caused by the sudden release of cell products. This, in turn, can often lead to life-threatening kidney failure. The most common serious side effects of CAR T-cell therapy include cytokine release syndrome (CRS). This is caused by the release of cytokines during the activation of the CAR T cell to kill the bound cancer cell, which then attracts more immune cells and activates these cells by releasing cytokines. This positive feedback loop can lead to a life-threatening "cytokine storm", i. e. excessive cytokine production that causes an immune response that can damage organs, and even lead to death. Emily Whitehead experienced a severe cytokine storm during her CAR T-cell therapy and was in intensive care for several weeks. Another serious disadvantage shown in most previous studies, including the two recently approved therapies, is that the CAR molecule that targets CD19 cannot distinguish between cancer cells and the immune system's normal B lymphocytes. As a result, combating the tumour might also cause the complete standstill of the patient's B cell-mediated immunity.

AVA Lifescience – The Theragnostic Company



From AVA's tumour-specific monoclonal antibodies to AVA's precision-guided, tumour-specific CAR T cells.

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Founded in May 2017 in Denzlingen near Freiburg, AVA Lifescience GmbH has found a way to avoid the serious side effects of this highly effective new immune cell therapy. The company develops innovative technologies for diagnosing and treating blood cancers; one of the company's unique selling points is a technology platform for producing functional antibodies of unprecedented specificity ("NextGenMonoclonals®"). Dr. Marcus Dühren-von Minden, Chief Scientific Officer (CSO) of AVA Lifescience, points out that these epitope-specific antibodies can be used to detect single amino acid changes in the target proteins. Such strictly tumour-specific antibodies can be used both for diagnosing and (in the case of a positive finding) in a second step for therapy following the humanisation of the antibodies. For highly personalised precision medicine applications, i.e. treatments targeted at individual tumour diseases, to be effective, therapy and accompanying diagnostics ("companion diagnostics") have to be combined. This is why Dühren-von Minden speaks of precision "theragnostics", as current CAR T-cell therapies do not meet precision medicine criteria. The tumour-specific NextGenMonoclonals® from AVA Lifescience specifically target anti-tumour antigen-binding regions to construct novel chimeric antigen receptors (CARs) and further develop precision-guided CAR T cells.

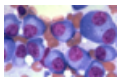
Tumour-specific CAR T-cell therapy could potentially reduce many of the problems mentioned above. Thus, what is known as "on-target, off-tumour toxicity" – i.e. the toxic effect on non-tumour cells (for example B lymphocytes, which have the same target molecule, i.e. CD19, as the cancer cells) – can be minimised. Dühren-von Minden explains that this means that treatment can be initiated at a stage when the tumour is still small. A smaller tumour mass also means that associated side effects such as tumour lysis syndrome and cytokine storm can be drastically reduced. Follow-up treatment to support the immune system is then unnecessary, and treatment costs can be reduced. CAR T cell therapy, developed on the basis of tumour-specific antibodies, opens up completely new treatment options, and for the first time a cure is possible.

Article

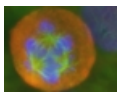
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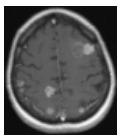
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