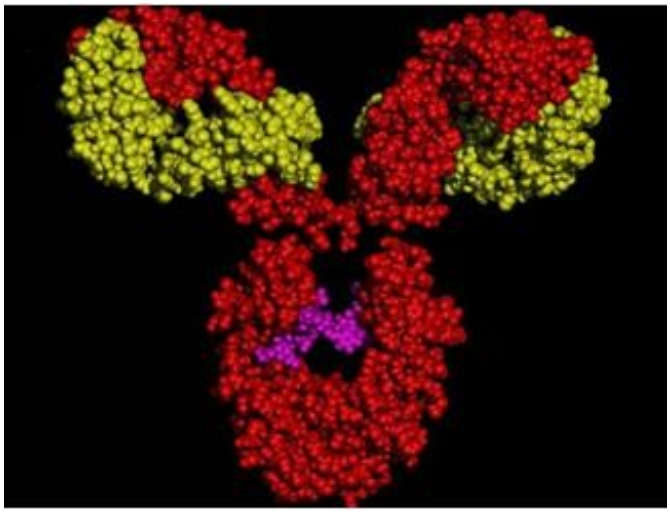
Cancer treatment adapted to individual patient requirements

There is still no treatment available for a number of non-Hodgkin B-cell lymphomas. Chemotherapy, which is the standard method of treating the lymphomas, has unpleasant side effects. Researchers led by Prof. Dr. Hendrik Veelken at the Freiburg University Medical Centre in cooperation with Freiburg-based CellGenix Technologie Transfer GmbH have developed a promising new treatment strategy. Results of the Phase I and the Phase II study, which has just been completed, show that the patients tolerate the new treatment very well and that the treatment has a long-term effect. As the treatment stimulates the body's own defences, it has to be tailored to the individual requirements of each patient.

The group of non-Hodgkin lymphomas comprises a diverse number of malignant diseases of the lymph system. Since the lymph nodes of affected patients do not contain any Sternberg-Reed cells, these cancers are not classified as Hodgkin disease. Non-Hodgkin lymphomas are the result of abnormal B-cells of the immune system starting to divide in an uncontrolled manner. Some of the B-cell lymphomas grow very rapidly. Although they can be treated fairly effectively with standard chemotherapies, these type of therapies have toxic side effects. Slow growing B-cell lymphomas are also hugely problematic because there is no effective treatment available. Therefore, it is essential to find new therapies. The researchers at the Freiburg University Medical Centre have developed one such new therapy.

Extremely variable target structures

"Our objective is to find a therapy that is associated with as few side effects as possible and that is able to repress tumours in the long term," said Prof. Dr. Hendrik Veelken from the Department of Internal Medicine I at the Freiburg University Medical Centre. "Our idea was to programme the patients' immune system in such a way as to be able to combat the tumour cells itself." The researchers had in mind a vaccination that sensibilises the immune system to cancer cells, thereby enhancing the body's ability to fight off the cancers. However, the problem with this method is that the immune system must be able to differentiate malignant B-cells from healthy B-cells. If it cannot do this, the immune system would then attack all B-cells, both healthy and malignant. This would cause the lymph system to collapse. The physicians led by Veelken based their new approach on a particular property of B-cells.



This is what the surface molecules through which the immune system recognises cancer cells look like. The variable parts that are specific for each B-cell are shown in yellow.

Immune cells normally recognise tumours thanks to specific molecules that are found on the surface of tumour cells. These molecules are a kind of molecular fingerprint. B-cells also possess this type of surface molecules, but they vary enormously: each B-cell and the lineage of its progeny has its own specific fingerprint. There are millions, if not billions, of different fingerprints. To make the immune system sensitive to a specific malignant B-cell lineage, it needs to be stimulated with a molecular fingerprint that fits exactly to the malignant cell lineage. It is then able to produce antibodies against the surface molecules. Since every individual person has a different malignant B-cell lineage that leads to cancer, the vaccination must be tailored exactly to the B-lineage affected.

"The method that we have been working on for around 14 years, involves several molecular biological steps and is technically very sophisticated," said Veelken. In principle, the physicians must first remove a tumour sample from the patient. Then they have to isolate the surface molecule that is specific for the particular B-cell lineage and multiply the number of molecules. And that's not the end of it. To be effective, the vaccine needs to be administered together with an adjuvant that helps to correctly position the vaccine in the body. Moreover, before vaccination, Veelken and his colleagues inject another substance under the patient's skin, which alerts the immune system and prepares it for the subsequent vaccination.

Precisely controlled workflow

The vaccine is expanded in E. coli bacteria. "We are currently the only group worldwide that produces a patient-specific vaccine in bacteria," said Veelken. "This makes the process a great deal faster than other methods." Veelken's team is supported in the production of larger quantities of vaccine by Freiburg-based CellGenix Technologie Transfer GmbH, a biotech company that was spun out of the Medical University Clinic in Freiburg. Ten years ago, CellGenix established a laboratory for producing the vaccine. This laboratory complies with good manufacturing practice (GMP) guidelines. "The production of a vaccine that is tailored to the specific requirements of each individual patient is a very time-consuming and costly process," said Prof. Dr. Felicia Rosenthal, Managing Director of CellGenix. The production of the vaccine under GMP conditions requires excellent laboratory equipment and an accurately controlled workflow. CellGenix took on the production of the vaccines for the clinical Phase I and Phase II trials. The Phase I trial was completed in 2006 and the results of the Phase II trial have just been submitted for publication.

All steps involved in the production of the patient-specific vaccination are carried out in the laboratory of CellGenix Technologie Transfer GmbH in Freiburg.

What were the results? The first investigations involving patients with late-stage tumours showed that the individualised vaccination barely had any undesired side effects. The majority of patients responded to the vaccination: the immune system induced the production of antibodies as well as specific immune cells against the tumour. The Phase II trial then focused on patients with so-called indolent lymphomas, i.e. tumours that are growing continuously but do not cause any long-lasting pain to the patient. The physicians treated two groups of patients: those who had previously undergone chemotherapy and whose tumour had decreased in size. Between seventy and eighty per cent of these patients produced an immune response. The second group consisted of people who had recently been diagnosed with a lymphoma, but who did not yet display any clinical symptoms. Such patients normally undergo chemotherapy when the tumour starts to cause problems. Prior to that, the negative side effects of chemotherapy are greater than its positive effects. Up to eighty per cent of these patients also produced an immune response. In about fifty per cent of these patients, the lymphomas disappeared and did not reappear after five years.

A vaccine with a future?

"Our vaccine means that the patients can avoid chemotherapy and that the disease does not reappear after a much longer time than usual," said Veelken. "At present we are however unable to say whether the vaccine has a long-term effect and whether all patients suffering from this type of lymphoma stand to benefit from the vaccination. Only 15 patients took part in our investigations, and this is too small a number to make conclusive statements." Since the results are very promising, the vaccine now has to be tested in a large randomised patient trial. Trials like this are very expensive. "CellGenix, which is a very small biotech company, is unable to produce

such large quantities of individual vaccines for financial reasons," said Rosenthal. A public funding programme would be one alternative, but no such funding is available at present. Although the cooperation between the University Hospital and CellGenix is strictly regulated by contracts that are standard for such type of cooperations, the German Federal Ministry of Education and Research (BMBF) still believes that a conflict of interest exists. The BMBF explained its unwillingness to fund a large-scale trial by pointing out that CellGenix was spun out of the department with which it is now working. "Although the spinning out of CellGenix is exactly the type of technology transfer to industry that the German government is seeking, they are nevertheless putting obstacles in our path," said Veelken.

Working in cooperation with a large industrial partner would be another alternative. However, Veelken believes that pharmaceutical companies are not particularly interested in producing individual vaccines. "The production of individual drugs for patients and the production of one and the same drug for all patients are two completely different business models," said Veelken. It would be a shame if 14 years of development work came to nothing despite the excellent clinical results obtained. Perhaps an investor will appear? In any case, this new treatment strategy is highly beneficial for patients.

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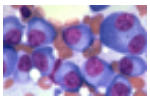

Cancer therapy and cancer diagnostics

Vaccine development