GENE THERAPY. NEW METHODS OF TREATING CANCER
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In the present day and age, practically every gene can be isolated and analyzed with molecular-biological methods. The growing awareness of causal genetic defects can be used for the diagnosis of a significant part of over 4000 human hereditary diseases. However, to a great extent, we are still a long way from utilizing this knowledge about the causes in the development of effective medication or treatment.

The new hope that the introduction of intact genes into human body cells can now directly cancel out the effect of the defective genes that cause illness ("somatic gene therapy"), led, first of all in the USA, now also in Europe, to the development of a total of more than 40 gene-therapy protocols. The treatment of relatively rare, life-threatening hereditary diseases such as the adenosine-deaminase defect, the mucoviscidosis, or the LDL receptor defect were initially in the foreground. The very latest research results point out that gene therapy could also possibly be used to fight more common illnesses such as cancer, which affect about a quarter of all human beings in the course of their lives.

One of the gene therapy approaches against cancer is based on the concept of strengthening the patient's immune defense system against the tumour. In the development of tumours such an immune reaction generally occurs in the initial stages. If this is not capable of directly shedding the tumour and destroying it, then the immune defence system becomes increasingly weaker as the development of the tumour progresses and is even actively suppressed by the body. Many of the conventional ways of treating cancer, such as surgery or chemo-therapy, which do help to remove large masses of tumour in the short-term, very often fail in the long-term because of the development of recurrences or the formation of metastasae. These could be prevented by reactivating the immune defence system against the tumour.

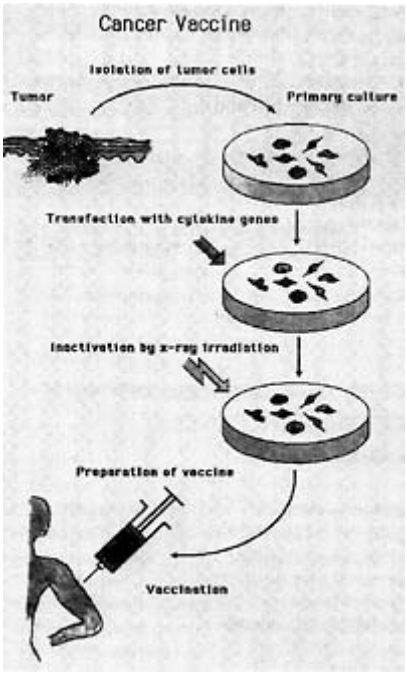
For this purpose, the patient should be administered with his own genetically changed tumour cells as a vaccine (tumour vaccine) in a splitdose irradiated form. First of all, genes are introduced into the tumour cells producing immuno-stimulated matter such as cytokine which entice the body's immune cells to the place of vaccination. A successful vaccination consequently activates and increases specific tumour cytotoxic T-cells — that is immune cells that circulate in the body of the vaccinated patient and which purposefully destroy individually dispersed tumour cells or micro-metastasae.

Tumour vaccine
Isolation of the tumour cells
Tumour Primary cultures
Transfection with cytokin genes Inactivation by X-ray treatment
Production of the vaccine
Vaccination

The prerequisite for such a therapy is an efficient and harmless method of introducing cytokin genes into cultivated cancer cells outside the body. A suitable gene transfer system was developed at the Institute for Molecular Pathology in Vienna in cooperation with our group, and the team headed by Prof. Max Birnstiel and that of Dr. David Curiel from the University in Chapel Hill, North Carolina. The starting point was the development of synthetic i.e. chemically produced complexes in the reagent glass. These contain the therapeutic genes in the form of nucleic acid (DNA) which are packed with transport proteins such as Transferrine.

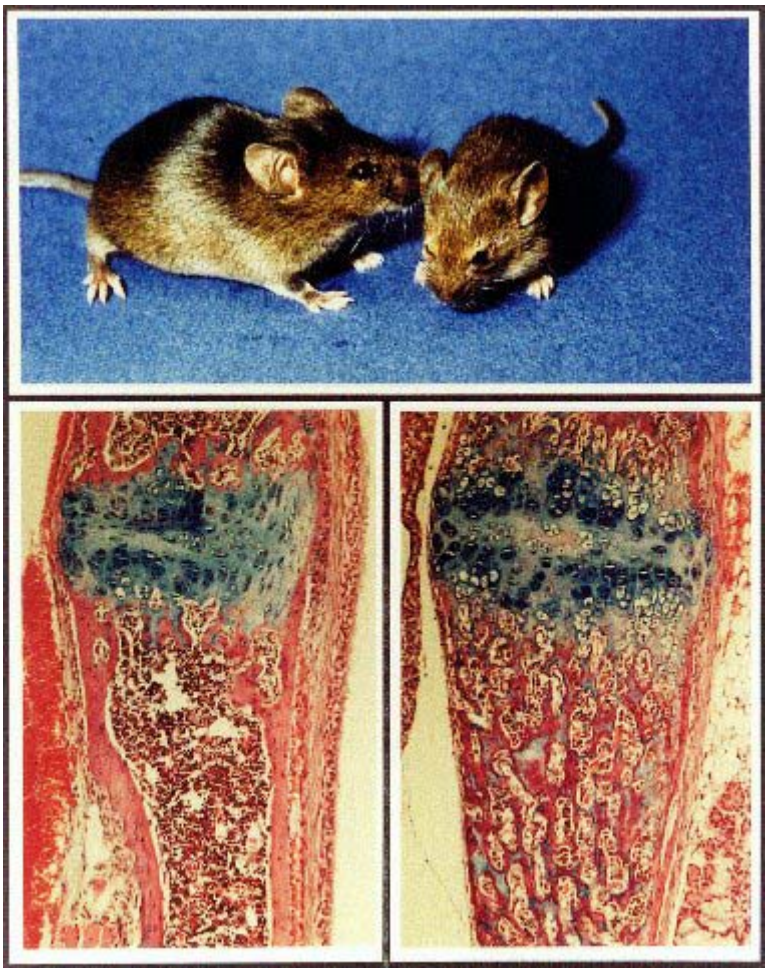
In doing so, the receptor-mediated endocytosis, a naturally efficient receptive mechanism for introducing the therapeutic genes into the cells, is possible.

These synthetic nucleic acid complexes have certain similarities with natural viruses, as far as the capacity of introducing DNA into the cells is concerned. The "artificial viruses" do have the big advantage that they cannot multiply within the cells like natural viruses. In addition to the completely synthetic viruses, we have also developed very efficient mixed forms, like a system containing dead adenovirus particles. Here, the DNA complexes are very efficiently transported into the cell and onto the nucleus of the cell. Then the therapeutic genes are transformed into messenger RNA which are transformed into the corresponding protein matter, the therapeutic protein.



This technique was tested on a series of different tumour cells e.g. on freshly isolated melanoma cells which cause malignant skin cancer. In a lot of cases, an efficient gene transfer was achieved. In the manufacture of a tumour vaccine (see Figure), the patient's fresh surgically isolated tumour cells are to be given the gene for the cytokin Interleukin-2. After irradiating these cells which are then no longer split, the cells are to be injected into the skin as a vaccine. At the point of vaccination these irradiated tumour cells produce great amounts of Interleukin-2 whereby a strongly tumour-specific immune response should be initiated (see above).

The efficiency of such tumour vaccines has already been shown in a mouse melanoma model. Here, mice were vaccinated twice with Interleukin-2-productive, irradiated mouse melanoma cells. Afterwards, vaccinated and nonvaccinated animals were given mouse melanoma cells. In every non-vaccinated mouse a tumour developed within two weeks, whereas all the vaccinated animals were protected against the development of cancer. As to whether such a gene therapy tumour vaccine can lead to an immunological additional form of treatment in human beings for the operative removal of the tumour to cure cancer, can only be discovered by treating cancer patients.



Phinotyp einer Maus mit c-Fos-Gen-Mangel. Gebremstes Wachstum und osteoperotische Knochen bei einer - /- Maus. (Institut für Molekulare Pathologie, Wien)