Immunotherapy of Cancer

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Most of us have had the flu once or twice in our lives. After being really sick for about one week, we recover without medication. It is common knowledge that the immune system can cure us from infections, but how is this possible? The first requirement is that our immune cells, the so-called T cells, are trained to recognize virally infected cells as foreign and different from our own tissues and cells (Fig 1).

This is possible since fragments from all proteins that are inside nucleated cells are continuously displayed on tissue type molecules (major histocompatibility molecules – MHC) on the cell surface, giving the T

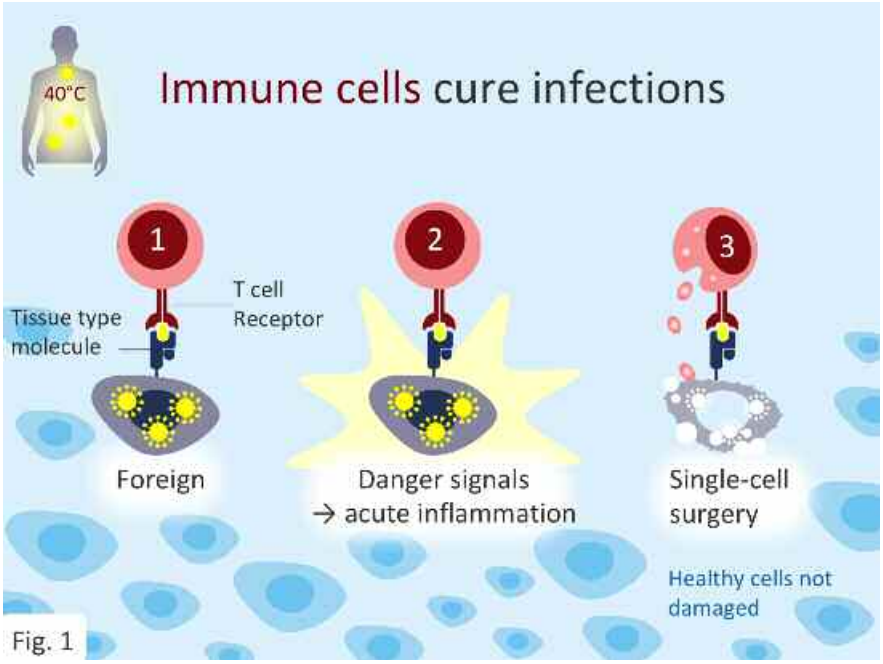

Fig. 1

cells information about what is going on inside the cells. The complex of the viral protein fragment and the tissue type molecule is recognized by some of the T cell´s T cell receptors. The second requirement is that these T cells *only* act and kill when what is seen as foreign is *also* seen as dangerous, because the viral infection causes an inflammation. We experience this inflammation as fever, a sore throat and tender lymph nodes during the flu. The inflammation gives rise to "danger" signals that activate and license the T cells that recognize the virally infected cells to kill them with the precision of single-cell surgery. This way, we can be cured from the infection without damage to the surrounding normal cells and tissues and without severe side effects. So why cannot T cells kill cancer cells with the same efficacy?

It is also common knowledge that in patients who have developed cancer, the immune system has lost the battle. The reason is that the cancer and the immune system have co-evolved in such a way that the immune system tolerates the cancer. Cancer often does not cause the right type of inflammation, which makes the immune system see the cancer cells as harmless foreign material that should be tolerated (Fig 2).

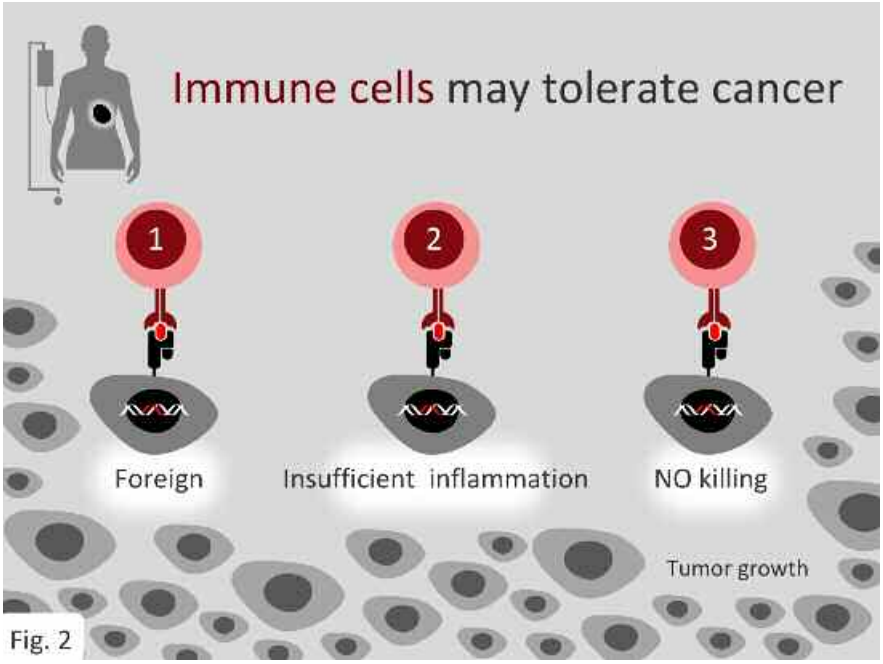

Fig. 2

The negative consequence is that the T cells do not kill the cancer cells. So why do we have such mechanisms? Similar mechanisms protect us against autoimmunity, which is a good thing. The lack of an immune response to cancer made scientists ask if they could vaccinate against cancer the same way as against infections. More than fifteen years of attempting vaccination against cancer, were largely unsuccessful.

But in 2013, one of the world´s most prestigious scientific journals - "Science" - ranked Cancer Immunotherapy as breakthrough of the year. This was due to the convincing clinical effects seen with new types of cancer immunotherapy in patients at this point.

One of the new breakthrough treatments was the use of so-called checkpoint inhibitors, which unleash the power of T cells in the patient. T cells can recognize fragments from altered proteins in the cancer cells as foreign. The altered protein fragments arise as a consequence of DNA damage causing DNA mutations. This can make the T cells kill the cancer cells. But the cancer cells can outsmart the T cells by exploiting inhibitory molecules on the T cells that suppress them (**Fig 3**).

In 2018, the Nobel prize in physiology or medicine was awarded to Jim Allison and Tasuko Honjo for discoveries that allowed T cell sup-

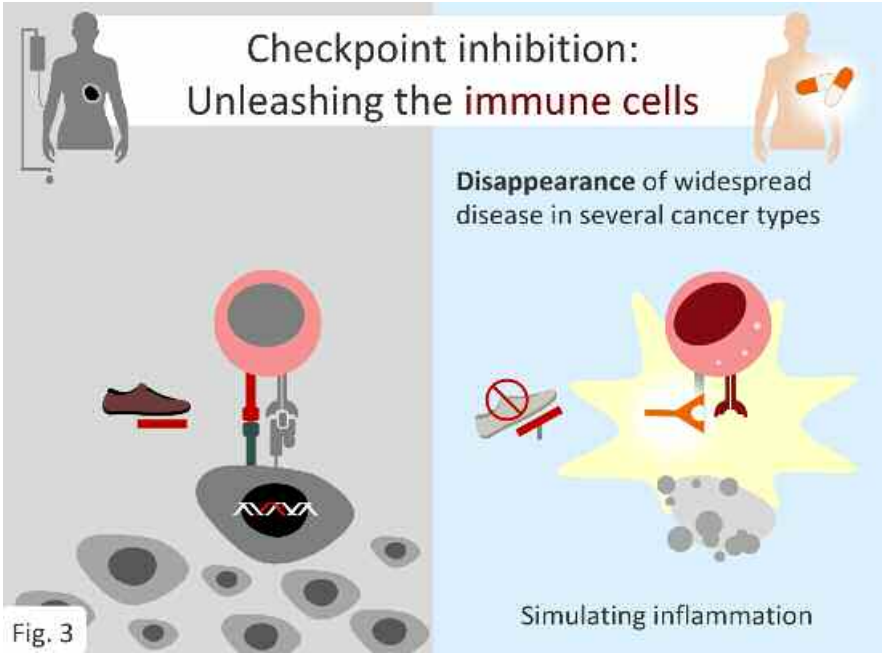

Fig. 3

pression to be reversed, making the T cells capable of killing cancer cells again (https://www.nobelprize.org/prizes/medicine/2018/press-release/). By use of antibodies, they could "block the brakes of the T cells" and make them activated. Very promising result with clinical response rates of 20–40 % have been achieved using checkpoint inhibition in patients with widespread disease from several cancer types, such as malignant melanoma and non-small cell lung cancer. A case in which a celebrity was cured of metastatic malignant melanoma by checkpoint inhibition, former US president Jimmy Carter, received much attention. But the majority of treated cancer patients are still not cured by checkpoint inhibition, and some cancer types are insensitive to the treatment. This calls for new strategies to be developed. In September 2018, there were 2,250 active trials testing checkpoint inhibitor agents anti-PD1/PDL1 in combination with various other anti-cancer agents, in attempts to improve the survival of patients. This represents a steep increase in trials relative to September 2017 (1,502 trials), demonstrating the large on-going efforts in this field (1).

One question that has drawn much scientific focus, is how frequently T cells "see" mutations in cancer. It is now clear that tumors with the greatest DNA damage and thus highest mutational burden, such as melanoma and non-small cell lung cancer, (2) are the cancer types that benefit the most from treatment with checkpoint inhibition. This represents indirect evidence that the patient T cells recognize mutations as foreign. A systematic search for the fraction of mutations that are spontaneously recognized by the patient`s own T cells out of the hundreds of mutations that on average occur in melanoma, demonstrated that very few were indeed seen by the T cells – 1.2% (3). This led me and my research team to ask the question if the poor immune response by patient T cells to mutations in the patient tumor could be overcome by healthy donor T cells. The rationale behind this hypothesis was that the T cells of healthy donors have not co-evolved with the patient tumor and would therefore be unaffected by any tolerizing mechanisms lessening the response. Indeed, we could demonstrate that healthy donor T cells recognized five-fold more mutations as compared with patient tumor-infiltrating T cells (4). Our improved method for identification of the T-cell receptors that mediate recognition of the mutations (5) could facilitate therapeutic use of mutation-specific, donor-derived TCRs by a strategy that is similar to CAR therapy, discussed below.

DNA mutations (or peptides encoded by them, so-called neoantigens) represent attractive therapeutic targets from the point of view that they are specifically expressed by the cancer cells and not by normal cells. However, it is now known that the large majority of mutations are unique to the individual tumor, and are thus not shared between patients. Any therapeutic strategy targeting mutations would therefore have to be strictly individualized. In addition, mutations are often heterogeneously expressed in the tumor. It would therefore be highly advantageous to identify therapeutic targets that are shared between patients. One example of a highly successful therapy directed at such a shared target is CAR 19 T cell therapy.

CAR 19 T cell therapy is based on a completely different principle than checkpoint inhibition. Here, the patient T cells are "armed" by equipping them with artificial immune receptors, so-called Chimeric Antigen Receptors (CARs) (Fig 4).

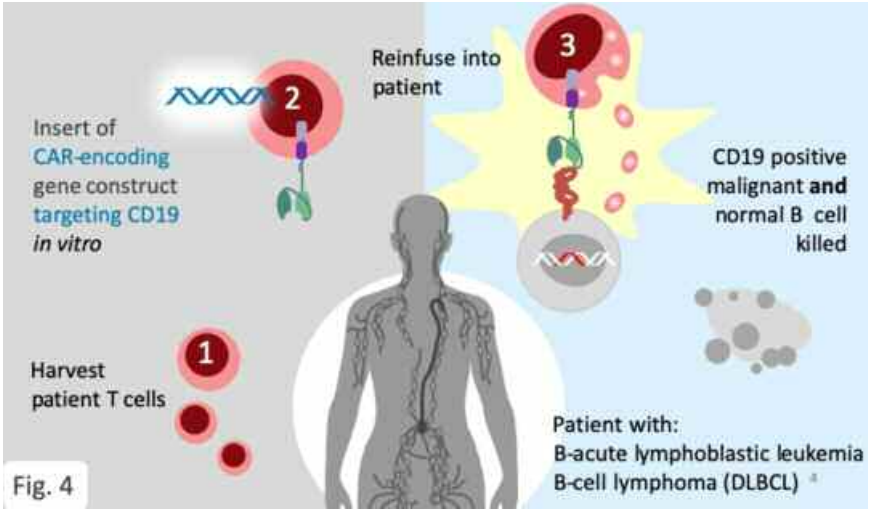

Fig. 4

CAR19 T cell therapy has revolutionized treatment of B-cell cancers, such as B-cell acute lymphoblastic leukemia (B-ALL) and Diffuse Large B Cell Lymphoma (DLBCL), curing up to 40% of patients that were previously incurable. The immune receptors are genetically transferred to the patient T cells in the laboratory by use of virus as a gene-carrier. The

immune receptors function as "heatseeking missiles" targeting the molecule CD19, specifically expressed on normal and malignant B cells. Upon re-infusion into the patient blood, the T cells can thus find the B cells and kill them. Since CD19 is expressed on both malignant and normal B cells, all B cells are killed alike, but we can live relatively well without B cells for many years as long as the immunoglobulins are substituted. CAR19 T cell therapy was approved by the American medicinal authority FDA for use in treatment of B-ALL and DLBCL in 2017. So, why can we not cure all cancers using the same concept?

The therapeutic success of CARs has not been extended to other malignancies, mainly due to lack of cell surface molecules that are cell-type specific *and* can be safely targeted. In contrast to CARs, which are based on antibodies for target recognition, T-cell receptors (TCRs) represent natural immune receptors that can recognize targets independently of subcellular location, as all proteins are continuously degraded and presented as peptides in complex with tissue type molecules on the cell surface. Therapeutic use of TCRs could thus vastly increase the number of candidate targets, as >90 % of cellular proteins are inside the cell. However, our T cells have been trained during development (thymic negative selection) so as not to react strongly to our own normal proteins. Otherwise we would all have autoimmunity. Thus, it is very difficult to identify TCRs from patients that with high efficacy can recognize their own shared, normal cell-type specific proteins. However, my team has - by use of the same mechanism that is responsible for transplant rejection - managed to identify TCRs that can reject single cell types (6, 7). We are currently exploring this approach for future use in immunotherapy of patients with various cancer types.

The number of clinical trials that are testing immunogene therapies, such as CAR19 T cell therapy and TCR T cell therapies, are rapidly increasing worldwide with close to 400 trials registered. The number of trials is now higher in China than in the USA, and Europe is lagging far behind. The large unmet medical need of the majority of patients with metastatic solid cancer succumbing to their disease demands for action. It is thus of utmost importance that medicinal authorities are standing shoulder to shoulder with scientists and clinicians to rapidly develop the necessary infrastructure also in Norway that can facilitate development of these promising new therapies.

Illustrations: Ellen Tenstad, Science Shaped

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