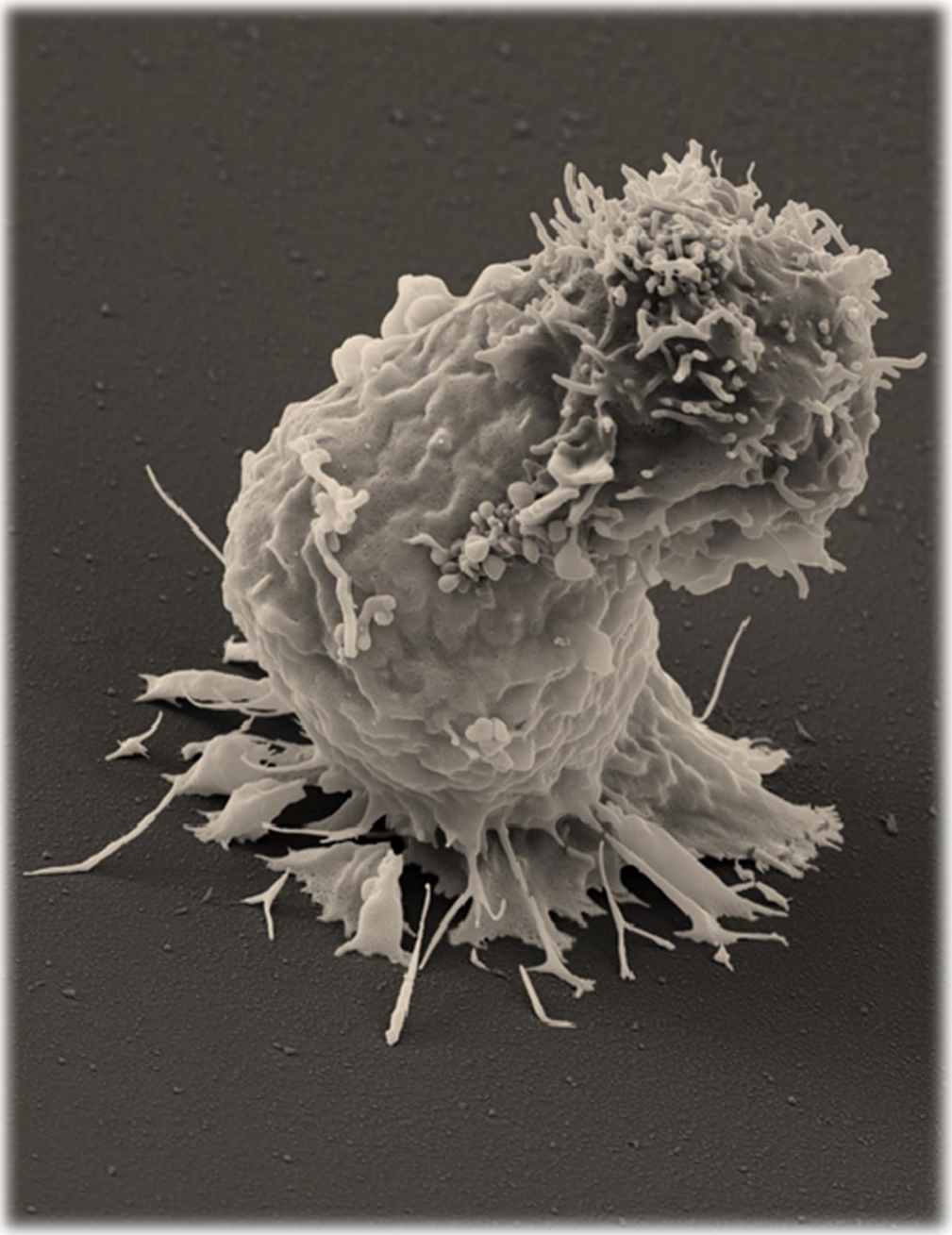
IMMUNOTHERAPY FOR CANCER: HOW AND WHEN?



Four women with terminal ovarian cancer underwent immunotherapy [(1)] even though they were not candidates for this type of treatment. Against all odds, their response was spectacular.

The question that arises is: why did immunotherapy work when this had not been foreseen at all. It is not known why the immune system differentiates between, and recognizes certain tumours.

Research often targets people who possess a biology that contravenes conventional generalizations.

The case of these four women is not representative, but exceptional. Exceptions are the source of the best ideas.

These four patients' tumours were hyper-calcaemic small cell ovarian cancer. This type of tumour is extremely rare. It usually debuts at the end of adolescence and early adulthood.

Douglas Levine, gynaecological oncologist at New York University Langone Medical Center is one of the few specialists in this type of tumour. A few years ago, he discovered that a single genetic mutation underlies this kind of cancer. The gene involved, oncogene, was given the name SMARCA4. This gene is involved in the growth of this and other types of tumours [(9)]. Genetic locus: 19q13.2, that is, short arm (q) of chromosome 19, position 13.2.

The SMARCA4 gene encodes the synthesis of a protein called hBRG1, which is a subunit that forms part of several protein complexes involved in the remodelling of chromatin, a complex of chromosomes and histone proteins. The remodelling of chromatin is fundamental in several processes that range from the repair of damage to the DNA, to its replication. [hBRG1 is the acronym for "human Brahma Related Gene type 1". Brahma is a Hindu god; the three-dimensional structure of the protein mimics the four arms of this god].

Via social networks, young women affected by this tumour were able to receive immunotherapy treatment without any objective medical justification. As a consequence of the treatment, their tumours collapsed immediately [(2)].

Conceptually, immunotherapy for cancer involves removing the barrier that many tumours create in order to by-pass T-cell attacks, the "artillery" of the immune system.

When tumour cells (such is the case of *hyper-calcaemic small cell ovarian cancer*) are only distinguished from normal cells by a single mutation, the difference in relation to healthy cells is insufficient to trigger an effective destructive attack from the patient's immune system.

Malignant cells from other types of cancer, such as lung carcinoma, colon-rectal cancer, and melanomas, have a high number of mutations. They are therefore excellent candidates for oncological immunotherapy.

In contrast, the neoplastic cells of other tumours, such as those of which affect the prostate, the pancreas, the breast, the ovaries, and many others, have few mutations.

These cells are not substantially different from their non-malignant counterparts and, consequently, do not respond well to anti-cancer immunotherapy.

Conceptually, the use of oncological immunotherapy to treat *small cell hyper-calcaemic ovarian cancer* was discarded because the cancer drift was linked to an isolated mutation.

Anti-cancer immunotherapy is based on monoclonal antibodies or fusion proteins which act as inhibitors of PD-1 receptors or their PDL-1 ligands. [PD, is the acronym for Programmed Death; and L, ligand]. A biomarker for the response to anti-PD-1 and anti-PDL-1 therapy is the *number* of malignant cell mutations, that is, the number of mutations in the tumour genome's area code. The validation of this biomarker has been carried out on 27 specific types of tumour. The "mutational load" was measured via an assay designed by Foundation Medicine. An excellent correlation was observed between the "mutational load" and the "objective response index" ($p < 0.001$). In addition, the correlation coefficient (0.74) suggests that 55% of the differences in the "objective response" can be explained based upon the "mutational burden of the tumour". Some tumours respond better than predicted (vg Merkel cell *carcinoma*), and others do not respond as well as might be expected (some types of carcinoma of the colon and rectum).

Even a formula has been developed to predict the response of a particular tumour to "anti-PD-1 and anti-PDL-1 therapy". This formula is:

$$Objetive\ Response = 10{,}8\ x\ lnX - 0{,}7$$

"X" being the number of mutations per 10^6 base pairs of DNA.

This formula attempts to estimate how a certain tumour will respond to the therapy of "checkpoint inhibitors" ("anti-PD-1 and anti-PDL-1"). With some types of cancer the theoretical prediction matched the clinical results. This happened in *basal cell skin carcinoma*, *cystic cerebellar astrocytoma*, *intestinal carcinoid tumours* and *sarcoma of lung parenchyma cells*.

For many cancerous processes there is a relationship between the number of mutations and the response to immunotherapy [(3)], but there are some exceptions. An unusual *Merkel cell carcinoma,* caused by a virus, responds to immunotherapy. Perhaps the presence of a virus acts as a trigger for the pharmacological activation of the immune system. [*Merkel cell carcinoma* is a rare and aggressive form of skin cancer described for the first time in 2008].

Mesothelioma also responds favourably, perhaps because asbestos (trigger of the neoplastic process) also make activation by the immune system feasible.

A similar situation occurs with some types of renal carcinoma, but nobody knows why.

The four women mentioned at the beginning of the article, with a confirmatory diagnosis of *hyper-calcaemic small cell ovarian cancer*, were treated with Nivolumab, despite the fact that, *a priori*, they were not candidates for this treatment. Surprisingly, their tumours collapsed. [Nivolumab is a human IgG_4 that binds to the PD1 receptor present in malignant melanoma' tumour cells [(4)], *non-small cell lung cancer* [(5)], *advanced renal carcinoma* [(6)] and *Hodgkin's lymphoma* [(7)]].

Eliezer M. Van Allen, a researcher at the North American Dana-Farber Cancer Institute, discovered that a mutated gene in renal carcinoma acted like a regulator of other genes. The regulated genes encoded proteins which the immune system could recognize as "defective." The mutation of the regulatory gene "deactivated" the genes. As the specific proteins were not synthesized, the response of the immune system was, therefore, blocked. Interestingly, the patients who responded to the immunotherapy had the mutation in that regulatory gene.

The researchers found this same phenomenon in some patients with *small cell hyper-calcaemic ovarian cancer*. One hypothesis to explain this blockage is that the immune system is "activated" or "deactivated" [pharmacologically] against cells in which genes are also "activated" and "deactivated", as a consequence of a specific mutation of the regulatory gene. In biopsies of the tumours, an abundance of T-cells was observed; indicative of an active immune response.

Because of these and other results, Pardoll and Padmanee Sharma, of M.D. Anderson Cancer Center, in Houston, Texas, decided to launch clinical trials.

Cancer immunotherapy is expensive, hence the importance of developing a test that distinguishes those patients who will respond to treatment in its simplest form. The work group of Padmanee Sharma is carrying out a study with this purpose in mind, financed by the Parker Institute. Tumours are biopsied to determine the degree of infiltration of T-cells. If it is sufficiently high, patients will be treated to enhance the anti-cancer activity of the patient's immune system.

When there is little penetration of T-cells into the tumour tissue, patients will receive an combination of two immunotherapy drugs in order to enhance the diffusion of T-cells, and not only stimulate those that have already been imbricated in the tumour tissue.

It is important to modify the concept of treatment: with immunotherapy, the tumour is not treated directly (as is the case with conventional chemotherapy [8]), but the patient's immune system is, *in fact*, the only true "medicine".

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