EDITORIAL
NEW CANCER THERAPIES BASED ON THE IMMUNE SYSTEM

In the 1890s, William Coley, a New York City surgeon, obtained spectacular results in some patients with sarcoma after inoculating their tumors with the erysipelas-causing bacteria. Since then, many cancer researchers have dreamt of developing therapies based on the exquisite specificity of the immune system to eliminate tumors without the toxicity associated with chemo and/or radiation therapy.

Currently, 120 years later, the list of accomplishments in this area begins to grow:

1. Three cytokines are used in anticancer therapies: high dose IL-2 in advanced melanoma and metastatic renal cancer, Interferon-α for hairy cell leukemia and as adjuvant therapy in melanoma in high risk of relapse, and the TNF-α for treatment of loco-regional disease, via extracorporeal perfusion, in melanoma and sarcoma.
2. It has been shown that Bacille Calmette-Guérin (BCG) instillation is an efficient treatment in recurrent superficial bladder carcinoma.
3. There are over a dozen monoclonal antibodies that are used in treating diverse types of tumors; of these, rituximab is considered an example of immune therapy because it targeteds the CD20 molecule expressed in the B lymphocytes and is useful in treating B-cell lymphoma.
4. The first therapeutic-cancer vaccine was approved in the United States by the Food and Drug Administration (FDA) in 2009. It is a recombinant protein representing a prostate-associat antigen Prostate Acid Phosphatase, (PAP) that must be loaded onto autologous dendritic cells prior to their infusion into the bloodstream.
5. Finally, in March 2011, the FDA approved the monoclonal antibody that blocks the CTLA-4 inhibitory receptor, which, when repeatedly administered, duplicates the median survival time of patients with advanced metastatic melanoma. It is the first treatment in many decades that manages to prolong survival rates in a type of cancer like malignant melanoma.

Hence, the study of the interactions between the immune system and cancer has been a continuous source of new anti-cancer therapies. The rate of discoveries has accelerated considerably over the last 15 years, as well as the rate of clinical trials to test new concepts and new immunotherapeutic products. Scientists, important sectors of big pharma and, most importantly, cancer patients, share great optimism on new promising therapies based on the immune system.

Conceptually, cancer immunotherapy rests on the postulate of the immune surveillance of tumors. This was clearly formulated in the 1950s by M. Burnet. This theory has been received with a variety of attitudes ranging from extreme enthusiasm to extreme skepticism. Nevertheless, a considerable amount of experimental results obtained from models of spontaneous tumors of growing sophistication has come to conclusively test this hypothesis. Currently, it is perfectly clear that the immune system specifically recognizes tumors and the outcome of this event is variable. In some cases, the immune system is capable of suppressing the tumoral progression, resulting in hidden, clinically silent tumors. In other cases, the tumoral progression coincides with the induction of specific immunological tolerance even during early stages of carcinogenesis. In humans, numerous studies have established the favorable prognosis associated with an infiltration of primary tumors by abundant memory T lymphocytes, particularly CD8 T lymphocytes. The likely meaning of this strong correlation is that the T lymphocytes that infiltrate the tumors represent a line of defense against tumoral progression that can protect the patient from a relapse during prolonged periods after surgical excision of the tumoral mass.

Recent progress in immunology is shedding light on the cellular and molecular mechanisms governing the initiation and maintenance of T lymphocyte responses, which protect the host from infections from viruses, intracellular bacteria, and metazoan parasites, as well as from tumors. A general model has gained wide acceptance according to which the immune system has developed mechanisms that permit it to recognize molecular patterns specifically associated with pathogenic microorganisms, as well as cell and tissue damage. It has also generated extremely specific systems allowing efficient discrimination between autologous and foreign components at the level of each cell of the economy. The specific recognition systems are the antibodies, capable of recognizing antigens in solution and the T lymphocytes equipped with T-cell antigen receptors (TCR) capable of recognizing internal antigens associated with the antigens of the major histocompatibility complex. According to

this model, the expectation was that tumor antigens recognized by the lymphocytes infiltrating the tumors should be derived from oncogenic viruses or from somatically mutated genes generated during of carcinogenesis. For this reason, there was general surprise when it became evident that most tumor antigens are actually self-antigens, derived from normal proteins. There are currently hundreds of tumor antigens identified, which are none other than combinations of short peptides derived generally from non-mutated proteins (10-25 amino acids) and class I HLA molecules (-A,- B, or -C) or class II (-DR, -DP, or -DQ). The former are recognized by CD8 T lymphocytes with cytolytic capacity and the latter by CD4 T lymphocytes capable of multiple immunoregulatory functions.

Knowledge on the identity of tumor antigens has opened new avenues of research. First, it has enabled monitoring of the anti-tumoral responses of T lymphocytes in cancer patients. A considerable wealth of information has been accumulated, which allows understanding the dynamics of these responses and understanding the reasons why tumors progress in spite of the presence of anti-tumoral immune responses. Second, the scientific community has embarked on the vigorous search for therapeutic vaccines against cancer. In this case, certain tumor antigens are selected as targets in the design of anticancer vaccine candidates. Until now, hundreds of phase I and II clinical trials have been conducted to test the safety and tolerance of new therapeutic vaccines. Two promising vaccines (MAGE-A3 and MUC-1) are being currently evaluated in terms of their clinical efficiency in treating lung cancer and metastatic melanoma, in randomized, double blind, placebo controlled phase III clinical trials. Third, this information has also inspired the optimization of novel cellular therapies consisting of *ex vivo* expansion of tumor-infiltrating T lymphocytes for a subsequent reinfusion of massive numbers (billions) of these cells. It is also possible to «reprogram» autologous T lymphocytes via transduction with a retroviral vector that carries TCRs specific for defined tumor antigens.

At the forefront of basic research, interest centers on understanding the multiple mechanisms operating inside the tumors and which impede an efficient anti-tumoral immune response. New targets have been identified for future therapies that should neutralize these immune-suppressing circuits and, thus, enhance the anti-tumoral response. Among these, there are inhibiting receptors such as CTLA-4, PD-1, Tim-3, BTLA, CD4 regulatory T lymphocytes, or myeloid derived suppressor cells.s

Certain enzymes are expressed at excessively high levels in the tumor microenvironment like Cox-2, IDO, INOS, and arginase. Their activity suppresses (for different reasons) the anti-tumoral immune response. Their inhibition in experimental tumor models has revealed a clear therapeutic potential. Finally, components of tumor stroma such as activated fibroblasts or blood neovessels are also valuable therapeutic targets.

In conclusion, cancer immunotherapy is an area undergoing development. Recently, new therapies have come about based on harnessing the immune system and it should be expected that in the future the number and efficiency of the new anti-cancer immune-therapies will continue to expand significantly.

In light of this, it is worth wondering how to prepare the medical and cancer patient communities for the new realities associated with the surge of these new therapies at the national level. It would also be worthwhile to address the Colombian scientific community about their attitude and willingness to participate in these latest developments.

Pedro Romero, MD
Ludwig Center for Cancer Research
University of Lausanne, Lausanne, Switzerland
e-mail: pedro.romero@unil.ch