Ital J Gender-Specific Med 2018; 4(3): 89-90

Anti-cancer therapy: the future is in "personalized" therapies

The contributions of James P Allison and Tasuku Honjo, Nobel prize-winners for Medicine 2018

Giuseppe Novelli[1], Lucia Novelli[2]

1. Department of Biopathology and Prevention, University of Rome Tor Vergata, Rome, Italy; 2. Department of Internal Medicine and Medical Specialties, Rheumatology Unit, Sapienza University of Rome, Rome, Italy.

The "one size fits all" approach is no longer in great favour, whether in fashion or Medicine - perhaps a reckless comparison, but useful in explaining the concept of uniqueness in humans. Our "biological book", i.e. our DNA, contains all the information about us, catalogued and well-engineered right from the first instant of conception, and it makes us unique. Good or bad luck decrees that a small variation, a tiny error in the sea of codes, can give rise to diseases of different degrees of severity. Tumours, for example, are a disease of the genome: and this is the starting-point for the pursuit of success in the immense struggle against the "Emperor of all Maladies", as Pulitzer Prize-winner and Indian physician Siddhartha Mukherjee defined it. So the applause for the recent awarding of the Nobel Prize for Medicine to the American James P Allison and Tasuku Honjo, from Japan, is resounding from all directions as a sign of the general approval of the entire scientific community.

Allison, an affiliate of the University of Texas and Honjo, of the University of Kyoto, received this high accolade from the Swedish Academy for understanding that "the immune system can be stimulated to attack the cancer cells, an entirely new therapeutic mechanism in the battle against a type of disease that each year claims the lives of millions of people and which constitutes one of the most serious threats to the health of humanity".

The huge value of the research carried out by these two scientists is therefore based neither in the immunology field nor in the two single proteins that they discovered, but rather in the fact of having understood how to activate these proteins and direct them to drive the response of the immune system. A hugely deserved Nobel Prize, not least for the scenarios that derive from that research: thanks to the discovery of CTLA-4 protein by Allison, it was possible to produce new more refined and specific immune-therapy drugs, which obtained excellent results and increased life in patients suffering from metastatic melanomas.

This Nobel Prize gives great hope to the whole research sector and is a comfort to those who with their work contribute to attaining the third of the objectives of sustainable development in the global Agenda, underwritten, reasserted and updated by the world's greatest: safeguarding the health and well-being of everyone of all ages.

The announcement of the Swedish Academy opens up the way, with a refreshed thrust, to a *customising* of treatment, i.e. an approach that banishes once and for all the concept of "one size fits all" and gives a fresh energy to the search of the right therapy for one particular tumour that has developed in that particular patient with her or his unique characteristics.

The immune system differs significantly between male and female with profound consequences for health and disease. Women develop more powerful immune responses than men in terms of both "non-self" and "self" antigens; this is translated into a lower susceptibility to infections, in a more effective response to vaccines but also into a higher frequency of autoimmune and autoinflammatory diseases compared to men[1]. Conversely, the risk of developing cancers is higher in men, in whom cancer fatality is almost double that of women[2]. These differences are rooted in the sex hormones which can have pro-inflammatory or anti-inflammatory activity, can modulate gene expression and create gender-specific immune processes which also influence the response to immune therapies[2,3]. For example, one of the genes discovered by the Nobel Prize-winners (PD-1) is modified in its expression by the menopause and by the hormonal status of the patients to significant effect.

We know little of the gender-specific effects of the effectiveness of the immune checkpoint inhibitors (inhibitors of PD-1, CTLA-4 or both) in cancer treatment. Recent research has indeed revealed the existence of a significant difference in terms of survival between males and females suffering from melanoma and lung cancer[3]. This should, in our opinion, stimulate research into immune therapy approaches that are differentiated according to gender. Gender dimorphism influences both innate and adaptive immunity, with a relevant impact on anti-cancer immunity[4]. Therefore the immunological differences between men and women might be relevant

to determining the response or resistance to therapies exploiting immune checkpoint inhibitors[5].

Lastly, it should never be forgotten that cancer is a disease of the genome: it is precisely the study of genome diversity, together with immune diversity, that will supply the key to the success of a therapy. "Genes possess their own ability to change", to borrow the words of the new Nobel Prize-winner Honjo. This points the way to the right road to overcome the great challenges in Medicine which still await us: giving value to research, supporting young scientists, reworking training programmes to make them more flexible, with cross-fertilisation and broadening of knowledge, opening up the journey to virtuous synergies within the context of *open science*. The academies which Allison and Honjo come from are the leaders in this field as they demonstrate their great value and are established as the homeland and nursery of brilliant minds and revolutionary discoveries.

References

1. Ortona E, Pierdominici M, Maselli A, Veroni C, Aloisi F, Shoenfeld Y. Sex-based differences in autoimmune diseases. Ann Ist Super Sanita 2016; 52 (2): 205-12.
2. Bereshchenko O, Bruscoli S, Riccardi C. Glucocorticoids, sex hormones, and immunity. Front Immunol 2018; 9: 1332.
3. Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, Viale G, Gelber RD, Goldhirsch A. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol 2018; 19 (6): 737-46.
4. Capone I, Marchetti P, Ascierto PA, Malorni W, Gabriele L. Sexual dimorphism of immune responses: a new perspective in cancer immunotherapy. Front Immunol 2018; 9: 552.
5. Botticelli A, Onesti CE, Zizzari I, Cerbelli B, Sciattella P, Occhipinti M, Roberto M, Di Pietro F, Bonifacino A, Ghidini M, Vici P, Pizzuti L, Napoletano C, Strigari L, D'Amati G, Mazzuca F, Nuti M, Marchetti P. The sexist behaviour of immune checkpoint inhibitors in cancer therapy? Oncotarget 2017; 8(59): 99336-46.

Conflict of interest statement: the Authors declare no conflicts of interest.