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EDITORIAL

# The 2018 Nobel Prize in Medicine for breakthroughs in targeting immune checkpoint inhibitors: a brief perspective

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*We shall not cease from exploration, and the end of all our exploring will be to arrive where we started and know the place for the first time.—T.S. Eliot*

## IMMUNOTHERAPY IMPACT

Cancer immunotherapy is based on the idea that the immune system can be stimulated to eliminate malignant tumors, as it can be stimulated against microbial infections. The first systematic use of this concept can be attributed to Dr. William B. Coley. Dr. Coley injected microbial organisms into tumors with therapeutic intent [1]. Since then, a better understanding of the immune system led to the production of a variety of immunotherapeutic interventions to treat cancer, with modest success. Such interventions include monoclonal antibodies, recombinant cytokines and cellular strategies including chimeric antigen receptors (CARs) [2]. In contrast to the injections of microbial organisms given with the intent to activate the immune system, these modalities of immunotherapy are essentially passive in their action [3]. The 2018 Nobel Prize in Physiology or Medicine was awarded jointly to James Allison, Ph.D. and Tasuku Honjo, M.D., Ph.D., for their independent work pioneering strategies that, in contrast to passive therapeutic strategies, enhance the immune response to tumor cells. These strategies dramatically increase the potential of the immune system as the fourth pillar of cancer treatment, together with surgery, chemotherapy and radiation therapy [4] (https://www.nobelprize.org/prizes/medicine/2018/summary). Dr. Allison and Dr. Honjo are basic research scientists, but their research quickly found clinical translation. Therapeutic outcomes of various forms of cancer that did not respond to more direct forms of therapy have significantly improved for certain patients using this specific type of immunotherapy. Checkpoint therapy can respond to non-refractory cancer with significantly better safety profiles than other therapies. In a minority of patients, long-term regression has been achieved. These results have given new life to the hope of better cancer control or cure [5]. Future cancer therapy is likely to be revolutionized with checkpoint therapy as foundational used with other therapeutics modalities.

## HISTORICAL SETTING

While other strategies of controlling cancer seek to remove tumors by eliminating them directly, immunotherapy works by harnessing the power of the host's immune system to control or eliminate tumors. A new modality of immunotherapy accomplishes this task based on inhibitors of negative regulators of the immune response known as immune checkpoint inhibitors (ICPis) [4]. The concept of controlling the growth of tumors by boosting the immune system response existed long before the separate works of Allison and Honjo [6, 7]. After decades of marginal successes in immunotherapy, detailed understanding of the mechanisms of regulation of T-cells laid the foundation for the realization of this new therapeutic strategy. Discoveries from Allison's group opened a path for the treatment of malignant melanoma through targeting a negative regulator of T-cell antigen recognition, an ICPi named CTLA-4 [6]. Honjo's group identified a different type of ICPi named PD-1 [7]. PD-1 is associated with effector cytotoxic cell dysfunction. Targeting PD-1 and its cognate ligand PDL-1 has more effective antitumor activity than does targeting CTLA-4. Targeting CTLA-4 is also associated with more side effects and a more limited therapeutic range of activity [8].

None of this work would have been possible without the enormous progress achieved in understanding how the immune system works. The initial concept of the immune system was one of a 'dichotomous' system divided between cellular and humoral components. These components were thought to be independently responsible for innate and adaptive or humoral responses [9]. Elie Metchnikoff and

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Paul Ehrlich received the 1908 Nobel Prize 'for their work on the immune system' (https://www.nobelprize.org/prizes/medicine/1908/summary). The conceptual dichotomy of the immune system based on Metchnikoff's empirical observations and Ehrlich's theoretical concepts of the immune system endured. It is not until recently that the interdependence of cellular and humoral components of the immune system has been fully appreciated. The realization of the immune system functioning as an integrated system of cellular and humoral arms finally brought a more definite understanding of how the immune system exerts its protective function [10]. Such protection finds its most obvious expression in our interactions with bacterial and viral agents. The understanding of these interactions stems from the seminal work of Louis Pasteur and Robert Koch, the giants on whose shoulders Metchnikoff and Ehrlich stood [11]. Recognition of the immune system as an integrated system with cellular and humoral arms has permitted viewing the immune response to tumors as similar to our interactions with bacteria and viruses [12]. This similarity implies the existence of fundamental rules of engagement. Knowledge of these rules of engagement allows the targeted use of the immune response to the benefit of our therapeutics efforts. A fundamental corollary of this understanding has been the realization that the immune system is subject to inhibitory controls at 'checkpoints'. As in other biological systems, these inhibitory controls maintain homeostasis [13]. The inhibitory controls of the immune system recognition and effector functions usually enable an effective response to bacterial and viral infections. However, tumors are composed of our own cells, making immunological recognition and effector functions substantially more complex. With a physiologically limited time of action, this complexity curtails our capacity for recognition of tumor antigens and effector interactions [12]. By blocking or inhibiting the action of these physiological inhibitors, we can enhance and prolong both the recognition and effector functions of the immune system when interacting with tumors.

## CURRENT STATUS OF CANCER IMMUNE THERAPIES

Clinical translation of work initiated by Allison and Honjo has so far resulted in regulatory approval of at least six antibodies and a combination of two ICPis as cancer therapies [5]. Current research in this area focuses on mitigating side effects and understanding the biological mechanisms underlying differential responses to ICPis therapy. This includes the critical distinction between the specific biological functions of ICPis that influence their effects on tumors. The two initial ICPis in clinical use are an anti-CTLA-4 antibody and an anti-PD1 antibody. There are fundamental differences in the biological functions of their targets that explain their effects when used individually and in combination. It is now clearly established that CTLA-4 is part of every immune response while PD-1 is induced. They also operate at very distinct junctions of the immune response. CTLA-4 is part of the immune priming response primarily affecting T-helper cells ($CD4^+$ cells). In contrast, PD-1 inhibits the T-cell receptor pathway, affecting primarily effector cells ($CD8^+$ cells). Due to these fundamental differences, combination has specific results that cannot be obtained just by using one treatment or the other [14]. There are multiple checkpoints that can exert positive or negative inhibition of the immune response at the priming level, effector level and possibly throughout the immune system. Understanding how to more effectively use this new knowledge is of great importance [14]. One of the better-defined aspects of ICPi activity is the neoantigenicity of the treated tumor. Neoantigenicity is a tumor biomarker of its susceptibility to the therapeutic effects of the ICPis. It has permitted identification of analogous situations in which there is sufficient difference between tumor and host tissue to allow the occurrence of an anti-tumoral response. In the case of renal cell cancer, there is an increase in the frequency of indels. This may be sufficient for a biological consequence equivalent to that of increased neoantigenicity. Thus, there is an opportunity to treat renal cell cancer with ICPis [15]. A similar situation occurs with tumors with defects in DNA damage repair leading to increased levels of neoantigens [16]. As often happens with any therapeutic intervention, there are unintended consequences associated with the enhanced activities of an immune system under the influence of ICPis, which may manifest clinically. The immune system may extend its effector activity to tissues other than the targeted tumor. Immune-related adverse events (irAEs) involve the immune attack of healthy tissues, an auto-immune event [17]. There have been cases of death due to serious irAEs (grades 3–5) [18]. Therefore, early diagnosis and prompt intervention are of outmost importance. There has been limited use of combinations of checkpoint immune inhibitors due to exaggerated immune responses, leading to increased severity of side effects [19]. Fortunately, the increased use of ICPis has permitted rapid identification of the most frequent irAEs as well as a mitigation of their severity [17]. In addition, the empirical management of these irAEs has allowed the establishment of guidelines for their subsequent treatment [20]. As expected, the control of these untoward effects of ICPis is fundamentally based on the suppression of the activated immune response by the judicious use of immunosuppressive agents and stopping ICPi therapy. In more serious cases, treatment involves the use of immunosuppressive doses of glucocorticoids alone or in combination with other broadly immunosuppressive agents [20]. Most recently, targeted mediators of specific immune responses such as secukinumab, an IL-17A cytokine inhibitor, have been successfully employed in cases where irAEs were severe enough to require combination therapy [21, 22].

Not all tumors respond with the same vigor to ICPis. The genomic structure of the targeted tumor may partially explain these differential responses. A recent study investigated differential responses to CTL-4 inhibitor in a large number of patients with malignant melanoma. An analysis indicated that, in contrast to aneuploid status, diploid status of the tumor is an important predictive biomarker of a vigorous response to ICPis. Together with tumor mutation burden, diploid status is considered to be among the most important potential biomarkers predictive of tumor response to ICPis [23]. Patients who are on glucocorticoids

prior to the initiation of therapy with ICPis are less likely to have a therapeutic response to ICPis. This is in contrast to patients who are started on glucocorticoids in response to irAEs after the initiation of ICPis treatment. In this latter group of patients, there is no apparent alteration of the therapeutic response to ICPis [24, 25]. Recent clinical experience with ICPis has shown that melanoma patients with an intestinal flora rich in *Faecalibacterium* and *Clostridiales* species tend to have a better response to PD-1 inhibitors. On the other hand, melanoma patients with intestinal flora rich in *Bacteroidales* species were more likely to be non-responders [26]. A similar observation has been made in patients with non–small cell lung cancer and urothelial carcinoma. Patients with these tumors and a flora rich in *Akkermansia muciniphila* responded better [27]. These results are in agreement with the proposal first made by Elie Metchnikoff, which asserted the microbiota influence in our health and disease status.

## KEY CHALLENGES AND OPPORTUNITIES REMAINING

Forging forward on the path of immunotherapy, key obstacles to overcome include the possibility of severe side effects, resistance to checkpoint blockade [28, 29] and the consistent discovery of new targets. Additional inhibitory pathways such as LAG-3, TIM-3, TIGIT, VISTA, B7/H3 and LILRB4 are now being targeted for cancer treatment [30, 31]. Thomas Khun affirmed that any real change of a paradigm is accompanied by the generation of new questions [32]. Some of the questions that have accompanied the advent of ICPis into the world of cancer therapeutics have found answers in surprising, dramatic responses of cancers for which therapeutic options were previously highly limited or nil. Many more new questions continue to be generated. The answers to these questions are bound to advance our fundamental understanding not only of cancer therapeutics but of how the immune system functions and of biology itself. It is not the goal of this perspective to outline each question that arises from the ICPis paradigm change, but rather to set the canvas with broad strokes for a more detailed painting.

One of the most important questions is why only a relatively small proportion of all cancers respond to ICPis? Another key question to be addressed is related to the need for cell physiological integrity in immunological mechanisms of negative feedback. The lack of response to ICPis in tumors with aneuploidy is an area in need of further studies. In general, the capacity to develop biomarkers to predict responses to ICPis is an important future area of research.

Another clinical observation in need of research relates to the circumstances surrounding the occurrence of irAEs. When administered, *a priori* steroids may inhibit the burst of activation of the immune system by the ICPis. In contrast, steroids administered after ICPis have been started, and the immune system has been activated can suppress the side effects of the activation of the immune system without significantly affecting therapeutic outcome. These observations are in need of better understanding and may influence the understanding of the physiology of activation of the immune system by an antigen. These questions can also overlap with questions related to the immune system response to vaccination and the effects of manipulation of the immune system prior to or after immunizations. Added to these considerations are questions related to the use of combinations of ICPis and of the potential synergism of enhancing antigen recognition with effector function.

The exploration of the use of a combinatorial approach of this new form of immunotherapy with established canonical therapies of cancer including surgery, radiotherapy and chemotherapy—not necessarily in this order—is of paramount importance for the future of cancer treatment [33]. Finally, we are coming to accept the fact that we are ecosystems, what has been described as 'self as a consortium' where the microbiota and the immune system interact influencing our physiological status [34]. ICPs are new to us but not to our species; they have been with us since ancient evolutionary times. This reminds us to continue to honor the Theodosius Dobzhansky aphorism that 'nothing in biology make sense except in the light of evolution' [35]. The advent of ICPis to the world of cancer therapeutics can be considered in its own right to be the equivalent of a Copernican Revolution in cancer therapy.

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### Conflict of interest statement

None declared.

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