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PERSPECTIVE

# The Era of Immune Checkpoint Therapy: From Cancer to Viral Infection—A Mini Comment on the 2018 Medicine Nobel Prize

Jia Liu[1] · Wen Pan[1] · Dongliang Yang[1]

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The 2018 Medicine Nobel Prize was awarded jointly to two immunologists, James P. Allison at the University of Texas MD Anderson Cancer Center in Houston and Tasuku Honjo at Kyoto University in Japan, who pioneered a new way to treat cancers (Ledford *et al.* 2018). Both Laureates have shown how so called "immune checkpoints" on T cells can be used to manipulate the immune responses so that T cells can efficiently attack cancer cells. Using the immune system to fight cancers has been investigated for more than a 100 years. Recent advances in cancer immunotherapy, particularly immune checkpoint blockade therapy have dramatically changed the therapeutic strategy against advanced cancers. Through inhibiting negative immune regulation, these approaches have demonstrated improved overall survival for patients with advanced cancers. Importantly, for some of the patients treated with such strategies, their tumors seem to totally disappear.

## Immune Checkpoint Therapy in Cancer

Most of the current immunotherapeutic success in cancer treatment is based on blocking the immune regulation function of critical checkpoints CTLA-4 (cytotoxic T lymphocyte associated antigen-4) and PD-1 (programmed cell death-1) by antibodies. In the 1990s, Allison and his colleagues studied the function of CTLA-4 and first discovered that CTLA-4 acts as a brake for T cell activation (Krummel and Allison 1995). They engineered an antibody that binds to CTLA-4 and blocks its function. *In vivo* administration of the antibody resulted in enhanced anti-tumor immune response and the rejection of tumors in mice (Leach *et al.* 1996; Kwon *et al.* 1997). Based on their pioneering findings, clinical trials using the new immunotherapy strategy were performed in the following years. A phase III clinical trial in 2010 demonstrated that Ipilimumab, a fully human monoclonal antibody that blocks CTLA-4, is sufficient to improve overall survival in patients with melanoma (Hodi *et al.* 2010), which is considered one of the watershed moments in the history of cancer immunotherapy.

Another critical immune checkpoint is PD-1, which was first identified and cloned by Honjo and his colleagues in 1992 (Ishida *et al.* 1992). Upon interaction with its ligands (PD-L1/PD-L2), PD-1 negatively regulates antigen receptor signaling of B cells and T cells, and thus serves as a negative regulator of immune responses. PD-1 was found highly expressed by tumor infiltrating T cells and PD-L1 was found strongly upregulated in a number of cancers where its expression often correlates with unfavorable outcomes. These findings make the PD-1/PD-L1 pathway an attractive target for immunotherapeutic interventions (Sanmamed and Chen 2018). Accordingly, preclinical and clinical studies have demonstrated the effectiveness of PD-1/PD-L1 blockade therapy in treating in a panel of cancers including melanoma, lymphoma, lung cancer, *et al.* (Brahmer *et al.* 2010; Hamid *et al.* 2013; Powles *et al.* 2014; Topalian *et al.* 2014; Garon *et al.* 2015). The clinical successes led to the FDA approval of antibodies targeting PD-1 (pembrolizumab, nivolumab) and PD-L1 (atezolizumab, avelumab) as second- or third-line treatment for various types of cancer when traditional chemotherapy or radiotherapy failed, including melanoma and squamous cell lung cancer, *et al.* These novel immune checkpoint targeting therapies illuminate new hope for cancer patients, in particular those who have lost the chance of surgical therapy and cannot bear the serious side effect of radiotherapy and chemotherapy.

✉ Jia Liu
jialiu77@hust.edu.cn

[1] Department of Infectious Diseases, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

## Immune Checkpoint Therapy in Chronic Viral Infection

In addition to immunosurveillance of cancer, a prime function of immune system is the defense against infectious agents, such as viruses, bacteria, and fungi, *et al.* Similar to that in cancer, T cells are exposed to persistent antigen and become exhausted in many chronic viral infections, such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infection. A cardinal feature of these exhausted T cells is over-expression of immune checkpoint molecules, such as CTLA4 and PD-1/PD-L1 (Wykes and Lewin 2018). Currently, control of both HIV and HBV requires life-long treatment, therefore, new strategies for treatment or cure for these viral infections are still urgently needed. The success of immune checkpoint therapy in cancer suggests that targeting these pathways could also be effective for treating chronic virus infection. As early as in 2006, Rafi and his colleagues reported that *in vivo* administration of PD-L1 blocking antibodies in mice chronically infected with lymphocytic choriomeningitis virus (LCMV) could rescue the antiviral function of exhausted CD8+ T cells to undergo proliferation, secrete cytokines, kill infected cells and decrease viral load (Barber *et al.* 2006). *In vivo* administration of PD-1/PD-L1 blocking antibodies restores T cell function and reduces viral loads in animal models of chronical retrovirus infection, such as simian immunodeficiency virus (SIV)-infected rhesus macaques (Velu *et al.* 2009) and Friend virus (FV)-infected mice (Dietze *et al.* 2013; Akhmetzyanova *et al.* 2015). Meanwhile, multiple *ex vivo* studies using PBMCs collected from chronic hepatitis B patients have demonstrated that PD-1/PD-L1 blockade could lead to enhanced HBV-specific CD8+ T cell response (Boni *et al.* 2007; Fisicaro *et al.* 2010; Zhang *et al.* 2011). In 2014, we for the first time reported the effects of *in vivo* administration of PD-L1 blocking antibodies on enhancing virus-specific CD8+ T cell immunity in chronic woodchuck hepatitis virus (WHV) infected woodchucks, a classic animal model for HBV infection research (Liu *et al.* 2014). In the study, we demonstrated that anti-PD-L1 blockade mono-therapy could not rescue WHV-specific T cell function, however, anti-PD-L1 blockade in combination with antiviral treatment and therapeutic vaccination, potently enhanced WHV-specific CD8+ T cell immunity. The triple-therapy strategy led to sustained immunological control of viral infection after antivirals withdrawal, WHsAg seroconversion and even complete viral clearance in some treated animals (Liu *et al.* 2014). Very recently, two studies reported in parallel that HBsAg-specific and global B cells also showed increased expression of PD-1 during chronic HBV infection, and *in vitro* anti-PD-1 blockade could partially restore the functional maturation of HBsAg-specific B cells (Burton *et al.* 2018; Salimzadeh *et al.* 2018). These studies suggested that PD-1/PD-L1 blockade therapy in chronic hepatitis B (CHB) patients might be able to improve both HBV-specific T and B cell functionality.

Despite the inspiring results observed in preclinical studies (summarized in Table 1), limited progress has so far been made in clinical trials using immune checkpoint therapy for treating chronic viral infection diseases (summarized in Table 2). Due to the obvious safety concerns, many clinical trials of immune checkpoint blockade in individuals with chronic viral infection are designed and performed in the setting of cancer presence. Recently, an open label phase I study of Nivolumab (anti-PD-1) with and without a hepatitis B vaccine GS-4774 in HBeAg negative chronic hepatitis B patients showed that Nivolumab was safe and well tolerated, and one treated patient underwent HBsAg seroconversion (Gane *et al.* 2017). A phase II study of anti-PD-L1 therapy (BMS-936559, by Bristol-Myers Squibb) in HIV-infected patients showed a clear increase in Gag-specific CD4+ and CD8+ T cells in two out of the six treated patients. This is the only trial of an immune checkpoint therapy in HIV patients without malignancy. However, the study was recently ceased due to retinal toxicity observed in a simultaneous macaque study (Gay *et al.* 2017). Recently, a database analysis presented at the European Society for Medical Oncology 2018 Congress reported the feasibility of using immune checkpoint therapy to treat HIV patients who develop cancer. In total there were 20 HIV-positive cancer patients received Nivolumab treatment, and none experienced immune-related adverse events. 24% of the 17 evaluable patients achieved a partial response to Nivolumab, which suggests that the overall response rate of HIV-positive patients seems to be similar to that of other cancer patients.

## Prospective

Chronic viral infection continues to be a major health problem worldwide. In many of viral infectious diseases, drug resistance remains a challenge, effective vaccine is unavailable or lifelong drug treatment is necessary. The huge success of immune checkpoint therapy in cancer has greatly inspired scientists to apply such strategies for treating chronic viral infection. However, to achieve a successful immunotherapy in chronic viral infection such as CHB, one has to deal with a major obstacle that the virus-specific immune response is strongly suppressed or silenced by the overwhelming antigenic viral load. Therefore, reduction of the viral antigen load is considered a key factor for the success of immune-based therapies. We suggest that combinations of antiviral drugs, therapeutic

**Table 1** Summary of preclinical studies in infectious diseases reporting benefits of targeting immune checkpoint.

| Pathway | Infection | Cells affected | Target species | Blockage | Effect | References |
|---|---|---|---|---|---|---|
| PD-1/PD-L1 | LCMV | CD8+ T cell | Mouse | *In vivo* | ↑ Proliferation<br>↑ Cytokines (IFN-γ, TNF-α, IL-2)<br>↑ Cytotoxicity (CTL, CD107a/b)<br>↓ Viral load | Barber *et al.* (2006) |
| | HSV | CD8+ T cell, macrophage | Mouse | *In vivo* | ↑ Proliferation<br>↑ Cytokines (IFN-γ)<br>↓ Viral load | Channappanavar *et al.* (2012)<br>Jeon *et al.* (2018) |
| | HBV/WHV | CD8+ T cell, B cell | Human/woodchuck | *In vitro*<br>*In vivo* | ↑ Proliferation<br>↑ Cytokines (IFN-γ, IL-2)<br>↑ Anti-HBs<br>↓ Viral load | Fisicaro *et al.* (2010)<br>Zhang *et al.* (2011)<br>Bengsch *et al.* (2014)<br>Liu *et al.* (2014)<br>Salimzadeh *et al.* (2018)<br>Burton *et al.* (2018) |
| | HIV/FV | CD8+ T cell, CD4+ T cell | Human/mouse | *In vitro*<br>*In vivo* | ↑ Proliferation<br>↑ Cytokines (IFN-γ, TNF-α)<br>↑ Cytotoxicity (granzyme B) | Porichis *et al.* (2011)<br>Palmer *et al.* (2013)<br>Seung *et al.* (2013)<br>Dietze *et al.* (2013) |
| | HCV | CD8+ T cell, CD4+ T cell | Chimpanzees | *In vivo* | ↑ Proliferation<br>↑ Cytokines (IFN-γ) | Fuller *et al.* (2013) |
| | SIV | CD8+ T cell, CD4+ T cell | Macaques | *In vivo* | ↑ Proliferation<br>↑ Cytokines (IFN-γ, TNF-α, IL-2)<br>↑ Cytotoxicity (granzyme B, perforin)<br>↑ Specific antibodies<br>↓ Viral RNA | Velu *et al.* (2009) |
| CTLA-4/CD28 | LCMV | CD4+ T cell | Mouse | *In vivo* | No effect | Barber *et al.* (2006) |
| | HBV | CD8+ T cell | Human | *In vitro* | ↑ Cytokines (IFN-γ) | Schurich *et al.* (2011) |
| | SIV | CD8+ T cell, CD4+ T cell | Macaques | *In vivo* | ↓ Cytokine (TGF-β)<br>↓ Viral RNA | Hryniewicz *et al.* (2006) |
| | HIV | CD4+ T cell | Human | *In vitro* | ↑ Proliferation<br>↑ Cytokines (IFN-γ, IL-2) | Kaufmann and Walker (2009) |

**Table 2** Summary of clinical trials targeting immune checkpoint in infectious diseases.

| Pathway | Infection | Trial phase | Effect | References |
|---|---|---|---|---|
| PD-1/PD-L | HBV | Phase I | One treated patient underwent HBsAg seroconversion | Gane *et al.* (2017) |
| | HIV | Phase II | Increased HIV-specific CD4+ and CD8+ T-cells | Gay *et al.* (2017) |
| | HCV | Phase I | Reduce HCV RNA | Gardiner *et al.* (2013) |

vaccines and immune check point therapy would be a promising approach to treat CHB. The following steps should be taken for the treatment: (1) Reducing viral load by antiviral treatment; (2) Inducing antiviral T cell and/or B cell responses by vaccinations; (3) Applying immune check point blockade to amplify and maintain the T and/or B cell functions. This triple therapy may hopefully allow for clinical efficacy of immune check point therapy to cure chronic HBV infection. Besides, it should also be recognized that immune checkpoints are involved in the regulation of peripheral tolerance to prevent autoimmunity, and thus blockade of the function of these proteins may also cause immune-related adverse events. The clinical outcomes of immune checkpoint therapy in infectious diseases remains to be determined. Nevertheless, the era of immune checkpoint therapy for cancer has arrived and the strategy may also revolutionize the treatment of infectious diseases in the near future.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Animal and Human Rights Statement** This article does not contain any studies with human or animal subjects performed by any of the authors.

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