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Editorial

A New Era for Immune Research

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Editorial

This is indeed an exciting time for research in immunology. Recent salient discoveries on several fronts are ushering in a new age of immune-therapeutics that hold great promise with the potential to provide options for patients who have little to none. These fronts include the discoveries of the programmed cell death protein-1 (PD-1) immune checkpoint pathway, the ROR γt-Th 17-IL-17 axis and its role in autoimmune disease, and the role of cannabinoids and their receptors in inflammation.

The discovery of PD-1 and its ligand, PD-L1 and PD-L2, quickly led to the realization that tumor cells utilize PD-1 ligand to down regulate T-cell responses and escape from detection and immune attack. This realization came from the finding that PD-L1 expression was detected in numerous cancers but not in normal tissues [1]. Furthermore, PD-L1 or PD-L2 expression by tumor cells was found to be associated with a worse prognosis and decreased survival. In both non small cell lung cancer and melanoma patients, higher levels of PD-1were observed on Tumor-Infiltrating Lymphocytes (TILs) than on circulating lymphocytes [2]. Finally, there was a negative correlation between tumor PD-L2 expression and the presence of CD8+ TILs in esophageal cancer [3]. All of these findings led to the rush of pharmaceutical companies to develop antibodies to PD-1 or its ligands for the blockade of the PD-1 checkpoint pathway. Of these antibodies, nivolumab (Bristol-Myers Squibb), a fully human IgG4 monoclonal antibody against PD-1, is the most advanced in the clinic. In the phase I study, the objective response rate was 31% for a median duration of two years in patients with advanced melanoma [4]. The median overall survival in nivolumab-treated patients was 16.8 months, and 1- and 2-year survival rates were 62% and 43%, respectively. In another study with nivolumab administered concurrently with Yervoy (anti CTLA-4 antibody) in melanoma patients, an overall response rate of 53% was observed [5]. This indicates that even greater efficacy may be observed when multiple checkpoints are targeted while adverse effects remain manageable. The PD-1 checkpoint is also being targeted in combination with vaccines and other immunotherapies to optimize clinical response. There are however, still questions remaining on targeting the PD-1 checkpoint. One important question is in regards to the mechanism responsible for anti-tumor responses in patients who have PDL-1 negative tumors.

The discovery of Th17 cells and their biology has significantly advanced our understanding of the pathogenesis of many human inflammatory diseases, thus opening a new window into the development of next generation of anti-inflammatory therapeutics. The involvement of Th17 cells and their cytokines IL-17A/F, IL-21, and IL-22 in inflammation became evident from studies demonstrating the presence of high amounts of these cells and associated cytokines in diseased tissue as well as the presence of high levels IL-17 in the sera of patients with autoimmune disease compared to individuals without disease. Furthermore, antibodies to IL-17 were able to alleviate the signs of disease in several animal models [6,7]. Since these initial studies, several antibodies targeting IL-17A (AIN457, LY2439821), IL-17F, IL-17R, and IL-23, have entered clinical trials and have so far shown significant efficacy in arthritis and psoriasis [8-10]. Surprisingly, however, targeting IL-17 with antibodies has shown mixed results in animal models of inflammatory bowel disease (IBD). Furthermore, results from clinical trials of brodalumab (anti IL-17R) and secukinumab (anti IL-17A) in Crohn's disease failed to improve disease symptoms, and even exacerbated disease in some patients [11] indicating that the role of Th17 cells and IL-17A appears to be more complicated than originally thought.

The discovery of the nuclear hormone receptor, RORγt, as the master regulator of Th17 cell differentiation and secretion of IL-17 revealed a therapeutic target for small molecules against the IL-23/IL-17 axis. Unlike antibodies targeted at specific cytokines, RORγt antagonists can attenuate the full spectrum of Th17 related cytokines. Furthermore, antagonists of RORγt are more likely to attenuate Th17 related cytokines as opposed to blocking these cytokines as is typical of antibodies. This would allow some level of IL-17 activity that is apparently needed in the gut for protection against fungal infection. For these reasons, RORγt antagonists may be effective when antibody therapies fail. This revelation has led to a highly competitive race among large pharma and start-up pharmaceutical companies to develop small molecule antagonists of RORγt. To date, there are numerous RORγt antagonists in pre-clinical stages of development and one developed by Orphagen and Japan Tobacco Inc. has recently entered clinical trials. These compounds not only show inhibitory activity against Th17 cell differentiation and IL-17 production, but have also demonstrated variable levels of efficacy in experimental autoimmune encephalomyelitis and psoriasis models [12,13]. Synthetic small molecules are, apparently, not the only source of RORγt antagonists. Interestingly, nature has also produced molecules that effectively antagonize RORγt. Recently, the natural product, ursolic acid (UA), has been found to selectively and effectively inhibit the function of RORγt, resulting in greatly decreased IL-17 expression in both developing and differentiated Th17 cells [14]. Furthermore, treatment with UA ameliorated experimental autoimmune encephalomyelitis thus suggesting that UA may be a valuable drug candidate or lead compound for the development of therapeutics for Th17-mediated inflammatory diseases and cancer. Based on these findings, very recently, The University of California Davis in collaboration with

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Visionary Pharmaceuticals has initiated a clinical trial of UA for the treatment of primary sclerosing cholangitis. The results of this trial are eagerly anticipated as are those from upcoming trials of synthetic RORγt antagonists in pre-clinical development.

The third frontier of recent significant advances includes important developments in cannabinoid pharmacology since the discovery of the cannabinoid receptors, CB1 and CB2. These developments include the actions of cannabinoids and their endogenous counterparts, the endocannabinoids on immune modulation. Exogenous cannabinoids have been shown to suppress T-cell-mediated immune responses primarily by inducing apoptosis and suppressing inflammatory cytokines and chemokines while increasing anti-inflammatory cytokines. For instance, the natural cannabinoid, 9-Tetrahydrocannabinol (THC), was found to induce apoptosis in naive and mitogen-activated splenocytes *in vitro* and that these THC-induced effects could be inhibited by CB2 antagonists [15]. In human studies, lung alveolar macrophages removed from marijuana smokers were compromised in their ability to produce TNF, granulocyte/macrophage colony stimulating factor and IL-6 in response to LPS stimulation [16]. Other recent *in vitro* studies have also shown the potent anti-inflammatory effect of synthetic cannabinoids CP55,940 and WIN55,212-2. Both CP55, 940 and WIN55, 212-2 down regulated IL-6 and IL-8 cytokine production from IL-1β-stimulated rheumatoid fibroblast-like synoviocytes, via a non-CB1/CB2-mediated mechanism [17]. Furthermore, several of these and other synthetic cannabinoids have shown efficacy in a variety of animal models [18]. For instance, in one study, intraperitoneal application of ACEA, a CB1-selective agonist, and JWH-133, a CB2-selective agonist, inhibited oil of mustard-induced colitis and subsequent symptoms such as induced distal colon weight gain, colon shrinkage, inflammatory damage, diarrhea and histological damage [19]. The results from these and similar studies have prompted initiation of clinical trials for the treatment of inflammatory diseases. A pilot trial of THC-rich cannabis given in the form of cigarettes for 8 weeks demonstrated significant clinical benefits over placebo in patients with Crohn's disease who did not respond to therapy with steroids, immunomodulators, or anti–tumor necrosis factor-α agents [20]. Currently, several synthetic cannabinoids are in clinical development including Resumab™ by Corbus Pharmaceuticals for rare inflammatory diseases.

It is clear from both *in vitro* and *in vivo* studies that cannabinoids have potent anti-inflammatory effects that are both CB1- and CB2-dependent and independent. Though much is known on the effects of cannabinoids on Th1 cells and their functions, little to no information is available on the effects of cannabinoids on NK cells, as well as Th17 and Treg cells, the balance of which, is a critical determinant of inflammation.

In conclusion, recent discoveries made on several fronts in the field of immunology have transformed our understanding of inflammation and cancer resulting in a new era for immune research that will potentially lead to valuable therapeutics that will fill many unmet needs.

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