The quality of an adaptive immune response is not based solely on specificity, but just as much the context in which the specificity is induced. Dendritic cells (DCs) play a fundamental role in the immune system by linking the innate and adaptive immune responses meanwhile continuously sampling the surrounding environment through among others pattern-recognition-receptors, which recognize specific chemical signatures mostly associated with pathogens. By doing so, DCs are key regulators of the specific responses of the immune system under both homeostasis and pathological conditions. For these reasons, DCs are attractive targets for immunomodulating drugs in various immune and inflammatory disorders. The present article reviews the use of a platform which exploits in vitro generated dendritic cells from human donors for prediction of the in vivo effects of e.g. immunomodulatory drugs, vaccine adjuvants or probiotics.

**In vitro monocyte-derived dendritic cells: a tool to mimic critical in vivo DC pathways**

As an alternative to isolating dendritic cells, which are present in blood only in very low frequencies, *in vitro* generated monocyte-derived dendritic cells (MoDCs) are widely used. The reason for this is that MoDCs can be generated in high numbers with a great plasticity from blood monocytes. Despite the wide use of MoDC in *in vitro* mode-of-action studies and clinical cellular therapy as e.g. approaches in cancer treatment, coherent evidence of a direct translation to the *in vivo* situation is still missing, though commonly suspected. However, the presence of dendritic cells derived from monocytes has been confirmed in inflammatory conditions *in vivo* (1).

The standard protocol used to generate human MoDCs includes stimulation with GM-CSF and IL-4 in order to differentiate monocytes towards immature MoDC. During differentiation, different sets of cytokines and surface markers are induced as a reaction towards the presence of particular other environmental factors, which the dendritic cell senses through its cytokine- and pattern-recognition-receptors (PRRs) among others. As a consequence, the environmentally matured MoDCs critically determine the type of immune polarization of e.g. T helper (Th) cells, when brought in contact with these – *in vivo* this polarization takes place in the lymph nodes after having sampled the surroundings of the periphery.

At Bioneer, we have optimized combinations of cytokines, chemokines, PRR agonists and prostaglandins, which in the best combinations and concentrations induce specific phenotypes of MoDCs. These phenotypes – consequently – have the ability to induce specific Th cell phenotypes, which impact the immune responses (2). The optimized combinations have resulted in cocktails, which are applied in Bioneer’s human *in vitro* MoDC platform to induce specific polarization patterns – the character of the cocktails depending on the relevant pathway in question (Figure 1).

**Dendritic and T helper cell phenotypes in autoimmune diseases, allergy and cancer**

In certain immune disorders, the environmental priming of DCs in the body has skewed the DC phenotype towards an unfavorable response resulting in allergy, autoimmune disorders or cancer associated with a matching unfavorable Th cell response (3). Under normal conditions, the locally or systemically induced Th cell phenotypes are crucial for optimal fighting of infections, cancers or raising self-tolerances. However, in several diseases, the Th response is out of balance. In autoimmune diseases like rheumatoid arthritis or psoriasis, there is a skewed Th1- and Th17-response. In type I allergy, there is a Th2-skewed response, and in cancer diseases, the response is generally associated with an extensive upregulation of T regulatory (Treg) phenotypes, which induce tumor-tolerance.

These unfavorable immune responses – when developed – continuously reinforce the imbalance by further inducing the overproduction of the mentioned troublesome Th cell phenotypes. So far, various immunosuppressive and immunomodulating drugs have been developed – small molecules as well as biologics – in order to modulate the imbalanced immune response in al-
Figure 1. Bioneer’s human in vitro MoDC platform, which mimics disease conditions, can be used to predict how test substances such as potential drugs, probiotics or vaccine adjuvants can influence DC and T cell plasticity and counteract disease phenotypes in vivo. The DC phenotypes associated with e.g. psoriasis, rheumatoid arthritis, allergy and caner are induced by the cocktail stimuli.

Allergy, autoimmune and transplantation diseases (e.g. anti-TNFα mAbs and Etanercept (TNFR2 ECD-Fc), Abatacept (CTLA4 ECD-Fc), Briakinumab (anti-IL-12 and 23 mAb), Omalizumab (anti-IgE mAb), corticosteroids, cyclosporines etc) (4). Recently, in cancer diseases, promising data are found when treating with a new class of biologics blockading checkpoint inhibitors (PD-L1, PD1, CTLA-4), thereby modulating and activating the immune system to circumvent Tregs and increasing the possibility of eradicating tumors.

Bioneers human in vitro MoDC and T cell platform

In Bioneer’s MoDC platform, the effect of potential drugs, probiotics or vaccine adjuvants can be measured on DC and T cell plasticity under mimicked disease conditions to predict how the test substances may counteract disease phenotypes in vivo (5). The non-cancer related pathways in the platform have been successfully validated by demonstrating that approved clinical drugs with known immunomodulating functions, such as dexamethasone, are able to suppress the cocktail-induced cytokine and surface molecule DC and T cell profiles associated with the disease pathway in question (2). The cancer related pathway is still under development and the blocking of checkpoint inhibitors (e.g. by Pembrolizumab, Nivolumab and Ipilimumab) are highly relevant in the present validation process to extend the platform.

References