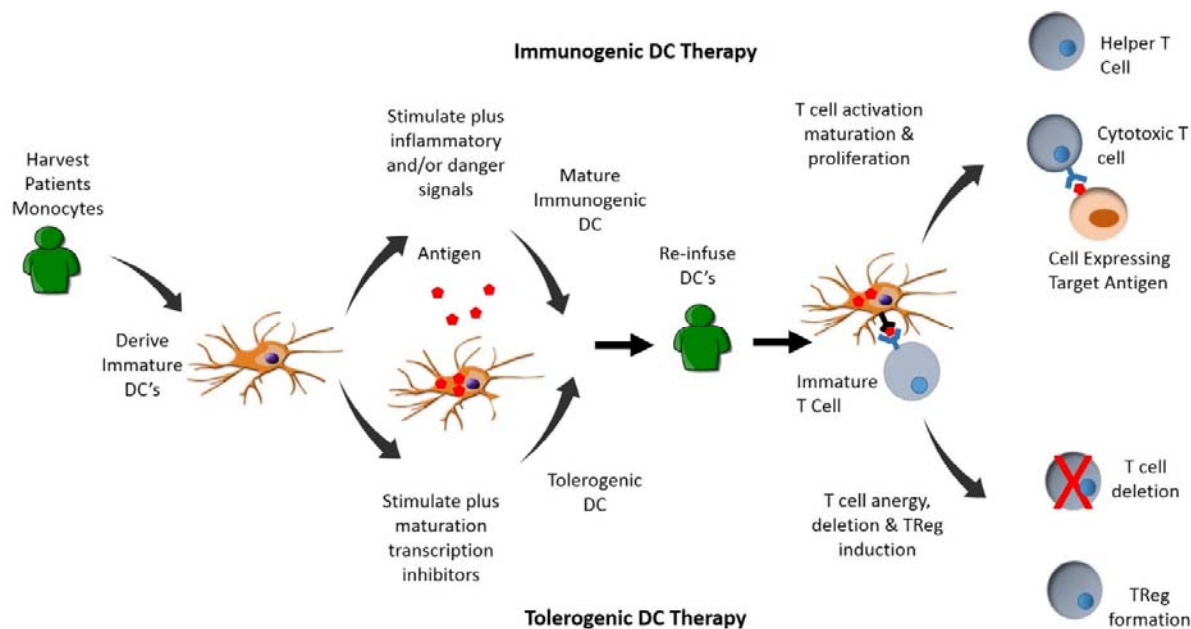


## Dendritic Cell Therapies

### BASIC FACTS

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The immune system comprises two arms; the innate immune system which is a nonspecific system and the adaptive immune system which is antigen specific. Dendritic cells (DC) provide the link between the two arms by presenting antigens to T cells, one of the effector cell groups of the adaptive immune response. Depending on the accompanying signals this allows a T cell with a matching receptor to either become activated and attack cells bearing the antigen target or to become tolerant and be deleted or non-reactive (anergic). The response of DCs to antigen is highly complex, and multiple factors can skew DC maturation towards either an immunogenic (ImmDC) or tolerogenic (TolDC) effector function. Scientists are manipulating these characteristics in attempts to develop immunocellular therapies that harness either the immunogenic or tolerogenic potential of dendritic cells (Figure 1). However, identifying the appropriate DC population and the potential plasticity of that population can make developing these therapies challenging.



**Figure 1** DC-precursor cells are harvested from the patient and used to culture immature DCs in vitro. To generate ImmDCs antigen is delivered via a variety of methods and the cells are treated, with typically a cocktail cytokines, to provide suitable stimulatory signals. For a TolDC therapy, drugs that suppress a critical transcription factor for DC maturation are provided in addition to the antigen. The therapeutic DCs are then re-infused into the patient to either activate the cytotoxic arm of the T cell response (ImmDC) or lead to T cell deletion and TReg formation (TolDC)

The majority of ImmDC therapies in development are targeted towards tumour cells or cells persistently infected with viruses such as HIV. The goal of the therapies is to induce both helper and cytotoxic T cell responses in order to eliminate the tumour or virally infected cell. Although anti-tumour immunity and clinical efficacy of DC based therapies have been reported, the majority of clinical trial results have been highly variable<sup>1,2</sup>. For oncology indications this is perhaps not surprising; priming T cells is difficult, the tumours originate from self and self-reactive T cells are usually deleted by negative selection or display low affinity and are subject to peripheral tolerance. In addition tumours employ numerous immune subversive strategies that can cause any T cells generated to be rendered tolerant, anergic or depleted from the repertoire. A systemic review and meta-analysis performed by Draube et al<sup>3</sup> for DC based therapies for prostate and renal cell cancer demonstrated an association between specific cellular immune response and clinical benefit. The analysis provided evidence on the relevance of dose (higher doses), mature phenotype and lymph node access (route of administration). The review also highlighted the need for future clinical trials to clearly characterise the DC, have clearly defined immune monitoring and criteria to assess clinical success.

Over the last 20 years DC therapies have been widely applied in clinical trials, particularly for the treatment of cancer. Looking across the EU and USA there is currently a single licensed DC therapy, Provenge® (sipuleucel-T) for the treatment of prostate cancer, which is approved in the US and has been granted marketing authorisation in Europe, with the product initially being available in Germany and the UK. Three further DC therapies are currently undergoing phase III trials in the EU and/or USA; Argos Therapeutics AGS 003 treatment for metastatic renal cell carcinoma, Northwest Biotherapeutics DCVax treatment for glioblastoma multiforme and NeoStem Melapuldencel-T treatment for metastatic melanoma. All these therapies are based on a patient's own DC. The DC are isolated by a procedure called leukapheresis and cultured in vitro with a source of tumour antigen (e.g. cancer cells or recombinant proteins). When re-introduced to the patient, the DC instructs the patient's T cells to target and attack the tumour cells. The complexity and cost (currently approximately \$90,000 for a three infusion treatment course) of DC therapies arises from the use of autologous products, the difficulties in standardising these, the logistical/manufacturing challenges of a therapy based on a patient's own cells and also to the complexity of the DC response to stimulus. This may have hampered developments particularly in the field of immunogenic DC therapies for oncology indications. It is likely there will not be a "one-size-fits-all" approach for such ImmDC therapies; instead the approach will be multifaceted with a need to tailor to the type and location of the tumour, the immune suppressive effects of the tumour environment and the immune status of the patient.

The discovery that DCs orchestrate T cell tolerance has opened up the possibility that DCs could also be used as an immunotherapeutic tool for diseases that are characterised by a breakdown in immune tolerance such as rheumatoid arthritis<sup>4</sup>. TolDC therapies are only just emerging in clinical trials (5 trials) and the three reported have been safe and well tolerated<sup>5,6,7</sup>.

It is currently unclear as to the duration of tolerogenic effect. It has been proposed that long lasting therapeutic effects will most likely be achieved with TolDC therapies that induce antigen-specific T<sub>Regs</sub> as these can provide ongoing immune regulation, such as inhibition of DC maturation, resulting in the generation of a regulatory feedback loop. If the effect of TolDC treatment is transient, repeat dosing may be required. As with ImmDC therapies there will be no single approach with clinical indication, method of tolerising DCs and local immunological environment all likely to impact the success of a given therapy.

Advances in the understanding of the biology of DC, the existence of distinct subsets with specific functions and molecular mechanisms used to regulate the immune response have helped better define what is required to elicit a therapeutic immune response; be that immunogenic or tolerogenic. In addition development of next generation technologies may help to meet the logistics and manufacturing challenges. This understanding should help unlock new opportunities for the development of dendritic cell therapies.

## REFERENCES

1. Engell-Noerregaard et al (2009) Review of clinical studies on dendritic cell-based vaccination of patients with malignant melanoma: assessment of correlation between clinical response and vaccine parameters. *Cancer Immunol Immunother* 58:1–14
2. Nierkens et al (2011) Harnessing Dendritic Cells for Tumor Antigen Presentation *Cancers*, 3(2), 2195–2213
3. Draube et al (2011) Dendritic cell based tumor vaccination in prostate and renal cell cancer: a systematic review and meta-analysis. *PLoS One* 6 (4):e18801
4. Hilken et al (2012) Tolerogenic dendritic cell therapy for rheumatoid arthritis: where are we now? *Clinical and Experimental Immunology*, 172: 148–157
5. Dhodapkar et al (2002) Antigen-bearing immature dendritic cells induce peptide-specific CD8(+) regulatory T cells in vivo in humans. *Blood*, 100(1):174–177.
6. Giannoukakis et al (2011) Phase I (safety) study of autologous tolerogenic dendritic cells in type 1 diabetic patients. *Diabetes Care*, 34(9):2026–2032.
7. Thomas et al (2011) Safety and preliminary evidence of efficacy in a phase I clinical trial of autologous tolerising dendritic cells exposed to citrullinated peptides (Rheumavax) in patients with rheumatoid arthritis. *Ann Rheum Dis*; 70 (Suppl 3):169.

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