

Tolerogenic Dendritic Cells as a cell therapy to prevent chronic rejection in kidney transplantation

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Introduction and objectives

Kidney transplantation (KT) is nowadays a routine procedure for people with end-stage renal disease. Treatment with **immunosuppressive (IS)** drugs has significantly decreased acute rejection rates. However, rates of long-term kidney loss have remained rather constant over the last decades due to the persistence of **chronic allograft injury**. Moreover, the lack of specificity of IS drugs renders the recipient susceptible to infections and cancer in the long-term. In this sense, **Tolerogenic Dendritic Cell (TolDC)**-based therapy represents an innovative and promising approach to achieve kidney transplant success through the induction of immune tolerance. The objectives of this review are:

- To understand the immune mechanisms underlying kidney chronic rejection and expose the hallmarks of IS therapy.
- To analyse the methods for *ex vivo* generation of TolDCs and their therapeutic potential in transplantation.
- To propose an experimental approach to improve TolDC therapy for the treatment of chronic rejection.

Methodology

The methodology consisted of a bibliographic search in Pubmed and GoogleScholar databases and immunology journals including *Nature Reviews Immunology*, *Annual Review of Immunology*, *Nature Immunology*, *Trends in Immunology*.

- The data was extensively analysed and contrasted.
- The main keywords used were, "chronic rejection", "kidney transplantation", "immune tolerance", "dendritic cells", "Tolerogenic dendritic cells".

Immunological phases of renal transplant rejection

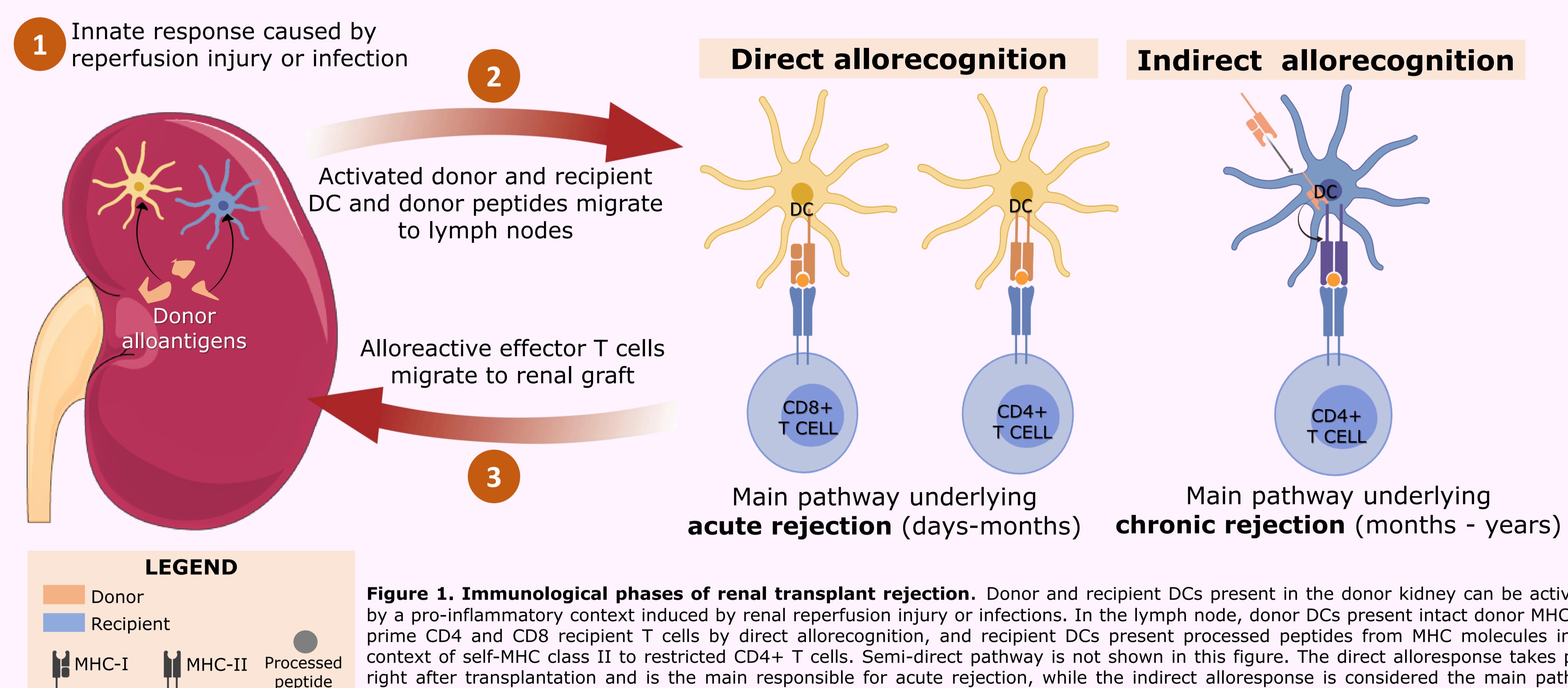


Figure 1. Immunological phases of renal transplant rejection. Donor and recipient DCs present in the donor kidney can be activated by a pro-inflammatory context induced by renal reperfusion injury or infections. In the lymph node, donor DCs present intact donor MHC and prime CD4 and CD8 recipient T cells by direct allore cognition, and recipient DCs present processed peptides from MHC molecules in the context of self-MHC class II to restricted CD4+ T cells. Semi-direct pathway is not shown in this figure. The direct allore cognition takes place right after transplantation and is the main responsible for acute rejection, while the indirect allore cognition is considered the main pathway causing chronic rejection. Adapted from [1].

State-of-the-art immunosuppression therapy for kidney transplantation

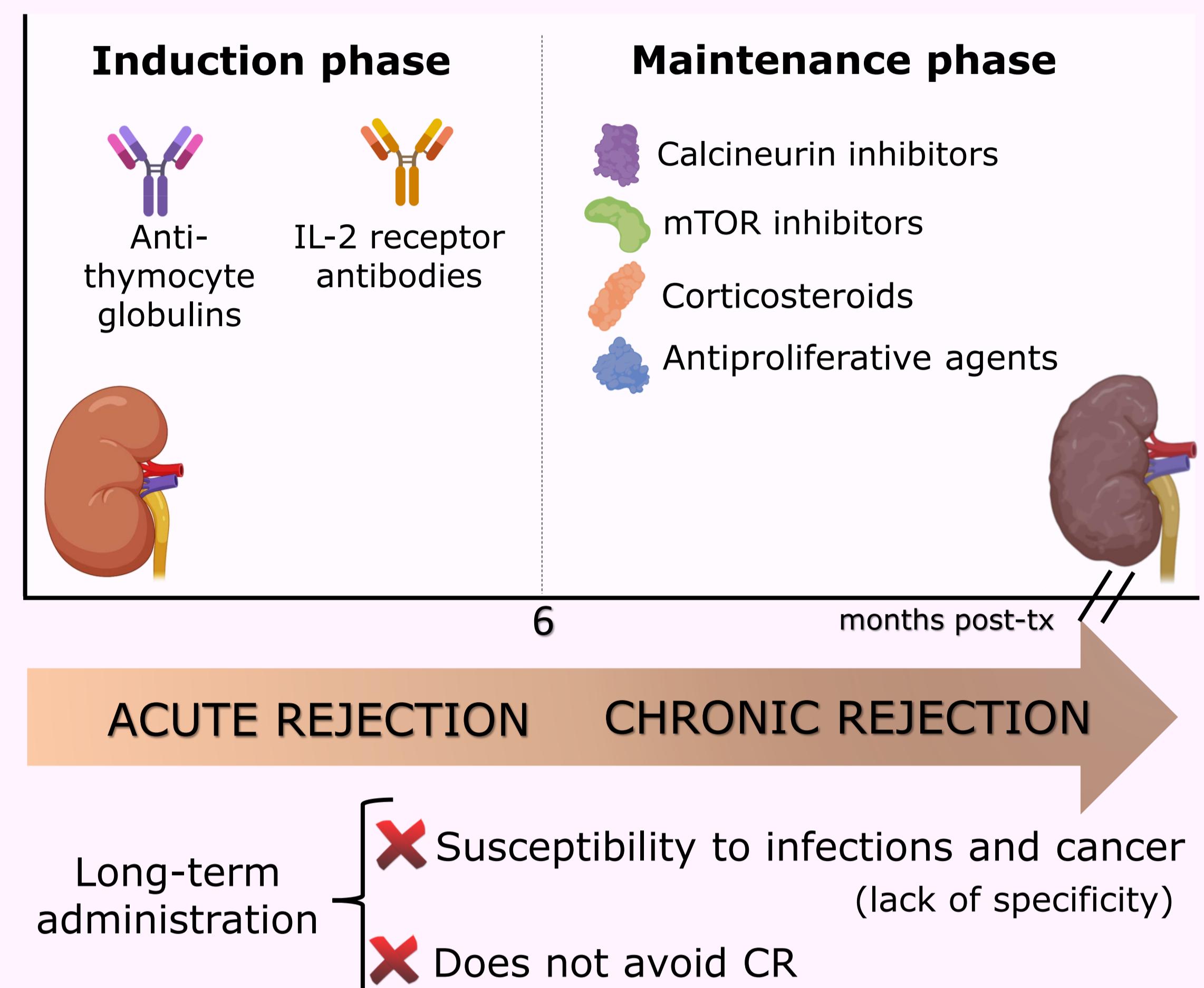


Figure 2. Current immunosuppressive treatment for kidney transplant rejection and long-term limitations.

Tolerogenic dendritic cells (TolDCs) generation and their therapeutic potential in transplantation

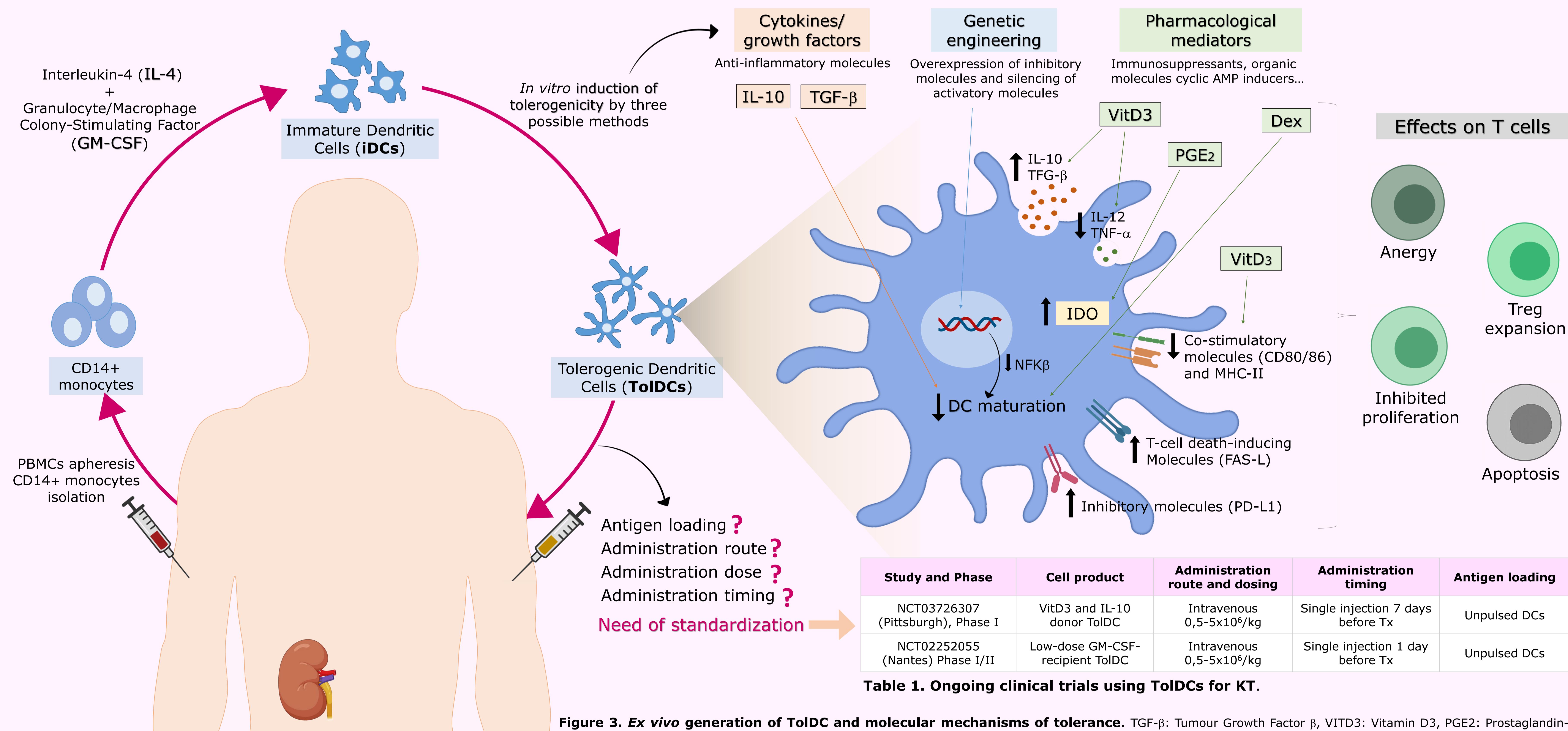


Figure 3. Ex vivo generation of TolDC and molecular mechanisms of tolerance. TGF-β: Tumour Growth Factor β, VITD3: Vitamin D3, PGE2: Prostaglandin-E2, Dex: Dexamethasone, IDO: Indoleamine 2,3-dioxygenase 1, Dex: NFKβ: Nuclear Factor κB, MHC: Major Histocompatibility Complex, PD-L1: Programmed Death-Ligand 1.

Experimental proposal: promoting tolerance to HLA-I peptides to prevent CR

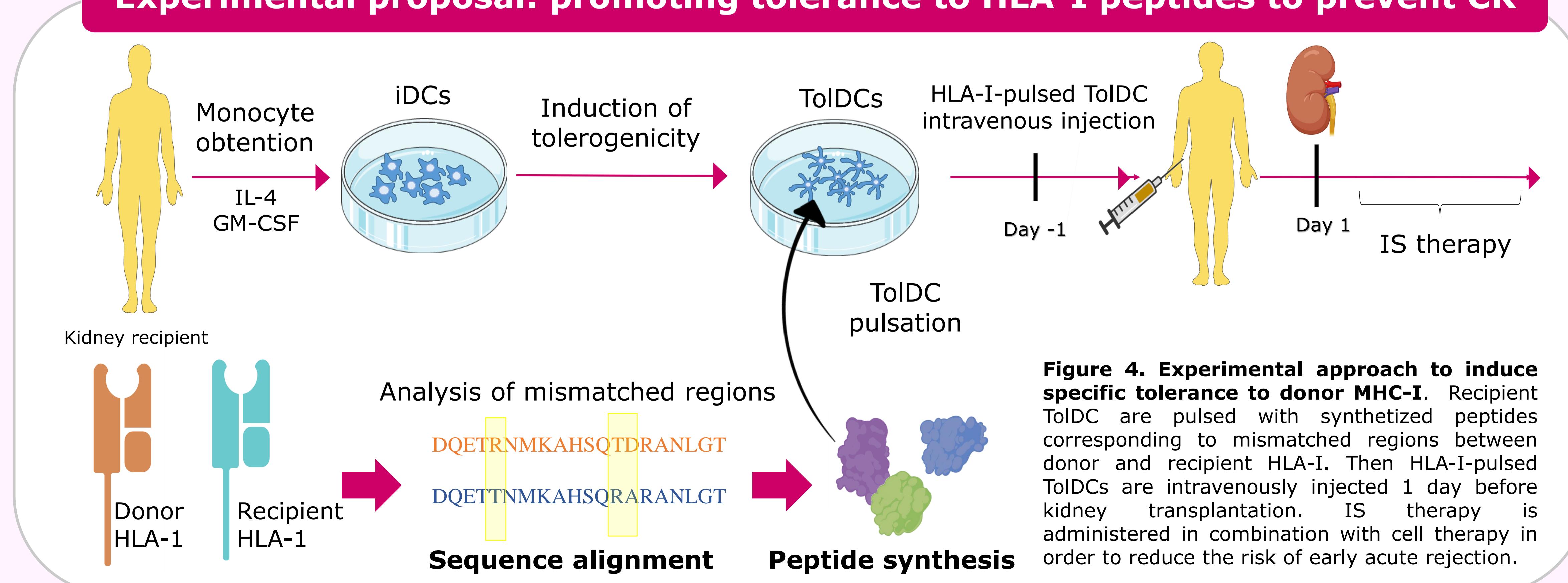


Figure 4. Experimental approach to induce specific tolerance to donor MHC-I. Recipient TolDC are pulsed with synthesized peptides corresponding to mismatched regions between donor and recipient HLA-I. Then HLA-I-pulsed TolDCs are intravenously injected 1 day before kidney transplantation. IS therapy is administered in combination with cell therapy in order to reduce the risk of early acute rejection.

Conclusions

- TolDC have demonstrated their therapeutic potential in transplantation, but we are still at the early beginnings of a highly promising therapy.
- Safe and efficient TolDC therapy would highly reduce the dependence on IS drugs, thus minimizing the incidence of infections and malignancies and improving long-term kidney graft survival.
- The main limitation of TolDC therapy is the lack of consensus regarding the optimal protocol for *ex vivo* generation. Further analysis of TolDC obtention protocols and mechanisms of tolerance will improve the potential of TolDC in transplantation.

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