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REVIEW

The time is now: moving toward virus-specific T cells after allogeneic hematopoietic stem cell transplantation as the standard of care

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Abstract

Adoptive immunotherapy—in particular, T-cell therapy—has recently emerged as a useful strategy with the potential to overcome many of the limitations of antiviral drugs for the treatment of viral complications after hematopoietic stem cell transplantation. In this review, we briefly summarize the current methods for virus-specific T-cell isolation or selection and we report results from clinical trials that have used these techniques, focusing specifically on the strategies aimed to broaden the application of this technology.

Key Words: *immunotherapy, stem cell transplantation, T cell, virus*

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has emerged as one of the best therapeutic options available for many patients with malignant and non-malignant diseases involving the hematopoietic system. The use of donors other than human leukocyte antigen (HLA)-matched siblings requires the depletion of host-attacking donor T cells to prevent graft-versus-host disease (GvHD). The broader use of alternative stem cell donor sources, such as unrelated donors, haploidentical related donors and umbilical cord blood (CB) have, however, resulted in an increased incidence of viral infections caused by the T-cell depletion strategies required to prevent GvHD. As a result, infection is one of the main causes of transplant-related mortality and morbidity in this setting (1).

Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and adenovirus (Adv) infections are particularly frequent among HSCT recipients and are often described as important risk factors affecting prognosis after HSCT (2–4). Although the introduction of sensitive viral screening techniques and pre-emptive treatment strategies have reduced deaths related to these complications, current antiviral drugs have some important limitations. First, depending on the drug, antiviral pharmacotherapy can result in bone marrow suppression and substantial toxicities (5,6) that are difficult to manage in patients who have undergone intense chemotherapy and radiation. Second, effective antiviral drugs do exist for CMV and EBV and can be beneficial, but the effectiveness of these agents in patients with Adv infection has only been suggested by non-randomized and uncontrolled clinical trials, and, in our experience, they are often not effective (7). Antiviral drugs—especially those used for CMV—can lead to late-onset CMV disease. Once the antiviral pharmacotherapy is removed, the late-onset CMV may be worse than the original reactivation because the use of these agents can delay virus-specific immune recovery (2). As a result, patients with viral complications may require multiple treatment courses, which is not only expensive, but drug resistance may also occur. In the case of

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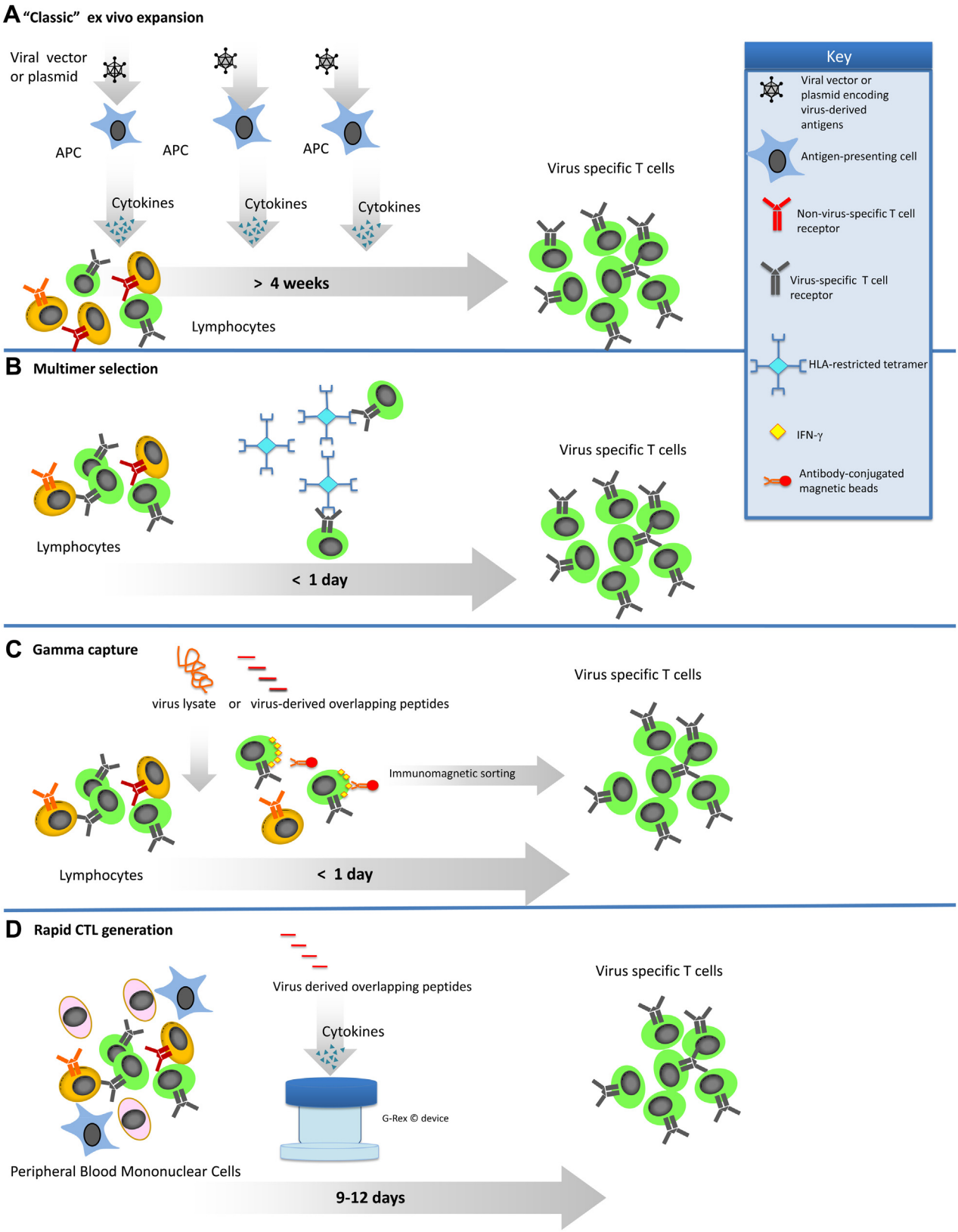

Figure 1. GMP-applicable approaches for the generation of virus-specific T cells. (A) In the classic *ex vivo* expansion, T cells are combined with APCs that have been transduced with either a viral vector or plasmids encoding the antigens of interest. The APCs are used to stimulate the T cells until cells of sufficient specificity and number have been expanded. (B) To prepare virus-specific T cells with the use of multimers, T cells are incubated with multimers that mimic the peptide:MHC binding of an APC. The T cells that bind the multimer are then isolated with the use of magnetic beads or fluorescence-activated cell sorting. (C) In the gamma-capture technique, T cells are activated use of the