interactions with Trp60D and Trp215, respectively. These structural similarities raised concern that aDabi-Fab may interact adversely with some of thrombin’s many substrates. Although the aDabi-Fab lacks proteolytic machinery, it might contain some structural elements that could, for example, compete in the exosite reactions of the protease so important for its function.\(^6\)

Unwanted anticoagulant or procoagulant activities of aDabi-Fab could compromise its safety in clinical use. It was therefore important to eliminate the possibility of these secondary interactions by demonstrating absence of binding of aDabi-Fab to physiological substrates of thrombin using surface plasmon resonance. Likewise, aDabi-Fab was shown to not directly influence platelet aggregation. Thus, aDabi-Fab would appear to competitively inhibit the binding of thrombin to dabigatran, while avoiding mimicking any of the exosite driven activities of thrombin. Schiele et al\(^7\) further supported this contention by demonstrating with thrombin-dependent in vitro functional clotting assays that aDabi-Fab is not active in the absence of dabigatran. Finally, it was shown that aDabi-Fab was also an effective in vivo antidote of dabigatran anticoagulant activity in rats, in which rapid reversal of anticoagulant effect in clotting assays was demonstrated.

Crucial to the success of this antidote to dabigatran will be additional studies of anticoagulant reversal in animal models of bleeding and, ultimately, in clinical investigation and trials of humans. In the meantime, this study does represent an important step in the development and use of the new oral anticoagulant agents. It shows that provision of a specific antidote is feasible and therefore suggests an effective means of controlling the anticoagulants in unpredictable clinical situations. If ultimately proven safe in human use, this will resolve what has until now been a pivotal limitation of these agents and provide an effective and safe strategy for situations in which immediate reversal of the anticoagulant effect is required.

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REFERENCES

manufacturing methodology to use dendritic cells genetically modified by an adenoviral vector encoding the full pp65 antigen. Their first approach was restricted to donors who were HLA A0201–positive and produced CTLs with restricted specificity that may have been predisposed to escape mutants. The second process, however, although it produces a broader immune response, is lengthy and requires live virus. Three alternative approaches may overcome these limitations. The first uses clinical-grade overlapping peptide pools derived from viral antigens to expand T cells with multiple antigen specificities. Alternatively, peptide-stimulated T cells can be isolated after interferon gamma (IFN-γ) capture. Both have shown encouraging responses as prophylaxis or treatment of CMV infection.

Finally, investigators have directly selected T cells that are reactive with CMV peptides by using magnetically labeled peptide multimers (streptamers). When CMV-specific T cells from the transplant donors were selected in this way and transferred to HSCT recipients with recurrent CMV reactivations, Schmitt et al observed reconstitution of CMV immunity and clearance of elevated CMV viral load. Although the limitations of this approach include the large volume of donor blood required for manufacturing, the requirement for donors to express HLA alleles for which viral peptides are available and to have a high frequency of circulating CMV-specific T cells, streptamer selection is being tested in a phase 3 randomized trial for CMV reactivation (NCT01077908).

The availability of several CMV-specific T-cell products manufactured with simpler methodology is finally allowing late-phase testing of CMV-specific CTLs to definitively show that they can prevent and treat CMV disease after HSCT, and Blyth et al have provided a roadmap for designing such studies by showing the importance of judicious choice of end points, the need for standard criteria for instituting and stopping antiviral drugs, and the desirability of incorporating comparative effectiveness analyses.

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Pharmacotherapy versus T lymphocytes for CMV

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