IMMUNOTHERAPY

Strain-specific antibody therapy prevents cytomegalovirus reactivation after transplantation

Jose Paulo Martins[1,2]*, Christopher E. Andoniou[3,4,5]*, Peter Fleming[3,4]*,
Rachel D. Kuns[1], Iona S. Schuster[3,4,5], Valentina Voigt[3,4], Sheridan Daly[3,4],
Antiopi Varelias[1], Siok-Keen Tey[1], Mariapia A. Degli-Esposti[3,4,5]†‡, Geoffrey R. Hill[1,6,7]†‡

Cytomegalovirus infection is a frequent and life-threatening complication that significantly limits positive transplantation outcomes. We developed preclinical mouse models of cytomegalovirus reactivation after transplantation and found that humoral immunity is essential for preventing viral recrudescence. Preexisting antiviral antibodies decreased after transplant in the presence of graft-versus-host disease and were not replaced, owing to poor reconstitution of donor B cells and elimination of recipient plasma cells. Viral reactivation was prevented by the transfer of immune serum, without a need to identify and target specific antigenic determinants. Notably, serotherapy afforded complete protection, provided that the serum was matched to the infecting viral strain. Thus, we define the mechanisms for cytomegalovirus reactivation after transplantation and identify a readily translatable strategy of exceptional potency, which avoids the constraints of cellular therapies.

Cytomegalovirus (CMV) infection and reactivation are associated with significantly reduced survival after bone marrow or hematopoietic stem cell transplantation (BMT) (1–3). The development of an effective CMV vaccine has proved problematic, and antiviral therapies are limited by toxicity and the emergence of drug-resistant CMV strains (1, 4). Efforts to improve the outcome of CMV infection have focused primarily on developing improved antiviral drugs (5, 6) or using adoptive T cell immunotherapy to mitigate the impact of infection and reduce disease (5, 7).

The risk factors that contribute to CMV reactivation in BMT have been examined in clinical trials but are associative in nature. A major limitation to improving CMV infection outcomes in transplant recipients is the paucity of preclinical animal models that faithfully represent the clinical situation in which CMV reactivation occurs post-latency. To address this unmet need, we developed mouse models of CMV reactivation after BMT. As in the clinical setting, we defined CMV reactivation functionally. Functional reactivation occurs after a period of latency and results in plasma viremia, as well as viral replication in target organs.

We used mice that were latently infected with murine CMV (MCMV) (Fig. 1A) as recipients in a major histocompatibility complex–disparate BMT model to investigate the role of conditioning and BMT on viral reactivation. Latently infected mice transplanted with T cell–replete grafts [graft-versus-host disease (GVHD) group] showed reduced survival compared with those that received bone marrow (BM) alone (non-GVHD group) (Fig. 1B). Mice that developed GVHD (Fig. 1C) demonstrated MCMV reactivation post-transplant (Fig. 1D). At 4 weeks post-transplant, reactivation occurred in 10 of 16 mice (63%) versus 2 of 12 mice (17%) in the GVHD and non-GVHD groups, respectively (Fig. 1E). Viral loads were detected in target organs and were significantly higher in recipients with GVHD (Fig. 1F). The lack of reactivation in the non-GVHD group suggested that conditioning and relative immunosuppression, modeled in this study by the absence of donor T cells, were insufficient to permit MCMV reactivation.

In clinical settings, the increasing use of rigorously T cell–depleted grafts in haploidentical stem cell transplantation has led to the reemergence of CMV as a major problem (8). This type of transplant requires intensive chemoradiotherapy combined with the administration of T and B cell–depleting antibodies, which results in the sustained loss of these lymphocyte populations (9). To model this clinical scenario, we used a haploidentical transplant system. In this system, conditioning and the GVHD response result in the loss of host B, T, and natural killer (NK) cells, as well as the poor reconstitution of donor B, T, and NK cells owing to profound type 1 inflammation (10, 11). Post-transplant, in the presence of GVHD, latently infected recipients (Fig. 1G) displayed significant viremia (Fig. 1H) and high viral loads in target organs (Fig. 1I). GVHD severity and survival during this period were not affected by latent infection (fig. S1). Using recipients latently infected with a recombinant MCMV carrying a LacZ reporter, reactivation was first detected at 3 weeks post-transplant (Fig. 1J). By week 4, replicating virus was present in multiple tissues (Fig. 1, K and L), including the lung and gut, which are common sites of clinical disease in patients.

During GVHD, immune reconstitution from the donor graft is compromised. Alloreactive T cells impair thymopoiesis, and peripheral expansion of T cells is also affected, as alloreactive T cells are more prone to apoptosis (12, 13). The B cell compartment is generally very slow to reconstitute because lymphopoiesis is also impaired (14). Consequently, the pathobiology of GVHD, combined with the immunosuppression required to treat GVHD, results in delayed immune reconstitution and long-term immunodeficiency (10).

CMV reactivation is thought to be largely controlled by antiviral CD8+ T cell responses, with NK cells further contributing to protection (15–19). Virus-specific CD8+ T cells were examined in a BALB/c→B6 transplant using tetramers that recognize recipient H-2K^b m38– and donor H-2L^d IE1–restricted responses. Early after BMT, recipient m38+ CD8+ T cells were detected only in non-GVHD conditions (Fig. 2A), whereas donor-derived IE1+ CD8+ T cells were not detected in either GVHD or non-GVHD groups (Fig. 2B). In the B6→B6D2F1 haploidentical transplant model, significantly lower numbers of both H-2K^b m38 (recipient and donor) and H-2L^d IE1 (recipient) CD8+ T cells were present in mice with GVHD (Fig. 2C). Thus, in the absence of donor T cell–mediated alloreactivity, recipient MCMV-specific T cells persist, potentially providing adequate protection against reactivation. We investigated this potential protection by imposing sustained immunodepletion to remove residual host and donor T and NK cells. TCRδ$^{-/-}$ grafts were used to examine protection conferred by γδ T cells. In transplanted mice without GVHD, despite the complete absence of T and NK cells (fig. S2), MCMV was not detected (Fig. 2D). Thus, in the absence of GVHD, T and NK cells (either recipient or donor-derived) and donor-derived γδ T cells are not essential for protection against MCMV reactivation. The lack of reactivation in mice without GVHD and depleted of all T cell subsets also indicates that conditioning and immunosuppressive therapy (the latter modeled here by profound immunodepletion) were insufficient to permit MCMV reactivation.

Our data suggest that humoral immunity may be sufficient to protect from viral reactivation in the absence of GVHD. Latently infected B6.μMt (μMt) mice, which lack mature B cells, were transplanted with T cell–depleted BM (TCD-BM) and depleted of CD4+, CD8+, and NK1.1+ cells. MCMV reactivation was detected in all μMt recipients, with high-level viremia in plasma (Fig. 2E) at day 14 post-transplant and substantial

[1]QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia. [2]School of Medicine, University of Queensland, Brisbane, Queensland, Australia. [3]Immunology and Virology Program, Centre for Ophthalmology and Visual Science, University of Western Australia, Perth, Western Australia, Australia. [4]Centre for Experimental Immunology, Lions Eye Institute, Perth, Western Australia, Australia. [5]Infection and Immunity Program and Department of Microbiology, Biomedicine Discovery Institute, Monash University, Clayton, Victoria, Australia. [6]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. [7]Division of Medical Oncology, University of Washington, Seattle, WA, USA.
*These authors contributed equally to this work.
†These authors contributed equally to this work.
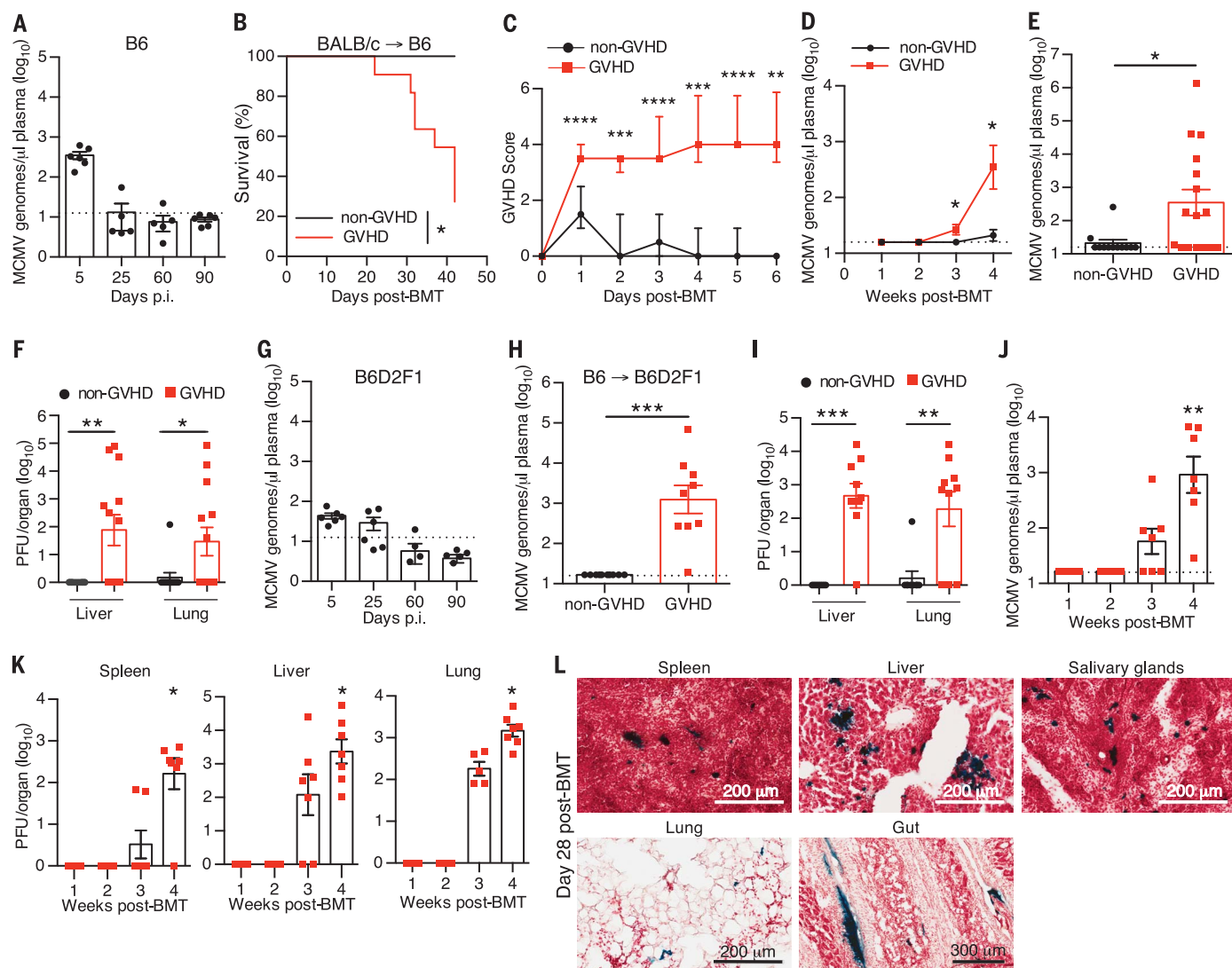‡Corresponding author. Email: mariapia@lei.org.au (M.A.D.-E.); grhill@fredhutch.org (G.R.H.)

Fig. 1. MCMV reactivation after BMT. (**A**) B6 (H-2^b) mice were infected with MCMV-K181^{Perth}; viremia (virus in plasma) measured by quantitative polymerase chain reaction at the indicated time points post-infection (p.i.) is shown ($n = 6$). (**B** to **F**) Latently infected (>90 days p.i.) B6 mice were lethally irradiated and transplanted with TCD-BM (non-GVHD) or BM + T cells (GVHD) from naïve BALB/c (H-2^d) mice. (B) Survival outcome (Kaplan-Meier analysis compared by log-rank analysis) and (C) GVHD clinical scores (median and interquartile range) are shown. Data are combined from two experiments with 3 to 6 mice per group per experiment (non-GVHD, $n = 7$; GVHD, $n = 11$). (D) Viremia over time; (E) viremia for individual mice at 4 weeks post-transplant (non-GVHD, $n = 12$; GVHD, $n = 17$); and (F) viral titers in target organs at weeks 4 to 5 post-transplant (non-GVHD, $n = 12$; GVHD, $n = 13$) are shown. PFU, plaque-forming units. Data in (D) to (F) are combined from three experiments with 3 to 6 mice per group per experiment. (**G**) Viremia in B6D2F1 mice at the indicated time points p.i. is shown ($n = 6$). (**H** to **L**) Latently infected B6D2F1 (H-2$^{b/d}$) mice were lethally irradiated and transplanted with TCD-BM (non-GVHD) or BM + T cells (GVHD) from naïve B6 (H-2^b) mice. (H) Viremia (non-GVHD, $n = 10$; GVHD, $n = 9$) and (I) viral titers in the indicated organs (non-GVHD, $n = 9$; GVHD, $n = 10$) at week 4 post-transplant are shown. Data are combined from two experiments with 4 to 6 mice per group per experiment. Kinetics of viral reactivation in B6D2F1 mice, assessed by measuring (J) viremia and (K) viral loads in target organs after transplant, are shown ($n = 7$ per time point). Data are combined from two experiments with 3 or 4 mice per group per experiment. (L) Tissue sections from transplanted B6D2F1 mice with GVHD. MCMV-infected cells in various organs are identified by X-gal staining. Data in (D) to (K) represent mean ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$ (Mann-Whitney U test). A dotted line represents the limit of detection.

viral loads in target organs (Fig. 2F) at day 16 post-transplant. μMt mice lacked MCMV-neutralizing antibodies pre-transplant (Fig. 2G). After transplant, they had low levels of MCMV-specific immunoglobulin M (IgM) and lacked MCMV-specific immunoglobulin G (IgG) antibodies (Fig. 2H). In addition to antibodies, T and NK cells may limit CMV reactivation. Indeed, MCMV

reactivation occurred only in immunodepleted μMt recipients (Fig. 2, I and J), and donor-derived humoral responses did not participate in protection (Fig. 2, K and L). Thus, humoral immunity is sufficient to limit viral reactivation after transplantation, with MCMV reactivation requiring the combined lack of antibodies, T cells, and NK cells.

Next, we defined the contribution of humoral immunity to CMV reactivation during GVHD. Serum from latently infected mice neutralized MCMV in vitro and contained high levels of MCMV-specific IgG pre-transplant (Fig. 3A). In transplanted mice with GVHD, MCMV-specific IgG levels were significantly reduced by day 28 post-transplant (Fig. 3B and fig. S3). MCMV-specific
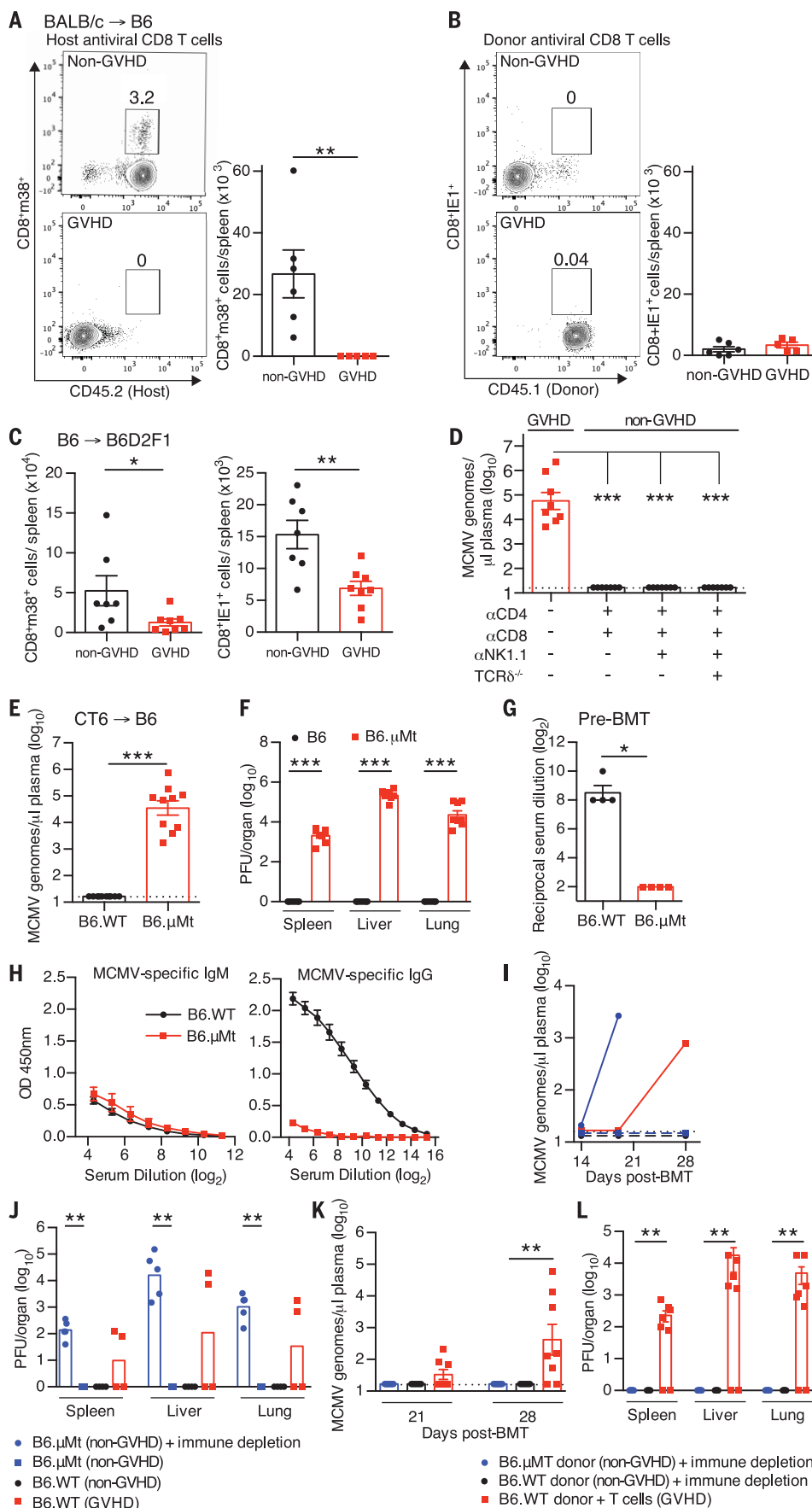
Fig. 2. Humoral immunity is required to prevent MCMV reactivation. Latently infected B6.CD45.2 mice were transplanted with BALB/c.CD45.1 TCD-BM (non-GVHD) or BM + T cells (GVHD). On day 14 post-transplant, the frequency and number of antiviral CD8+ T cells were assessed by flow cytometry. Representative flow plots and total number of (**A**) recipient-derived, virus-specific m38+ CD8+ T cells or (**B**) donor-derived virus-specific IE1+ CD8+ T cells (non-GVHD, n = 6; GVHD, n = 5) are shown. The data are representative of two experiments. (**C**) Latently infected B6D2F1 mice were transplanted with TCD-BM (non-GVHD) or BM + T cells (GVHD) from B6 mice. Virus-specific m38+ and IE1+ CD8+ T cells enumerated at day 14 post-transplant (non-GVHD, n = 7; GVHD, n = 7) are shown. Data are combined from two experiments with 3 or 4 mice per group per experiment. (**D**) Latently infected B6D2F1 mice were transplanted with TCD-BM from B6.WT or B6.TCRδ−/− mice. The indicated depleting antibodies were administered after transplant. Viremia at 4 weeks (GVHD) or 6 weeks (non-GVHD) post-transplant (non-GVHD, n = 7; GVHD, n = 8) is shown. Data are pooled from two experiments with 3 or 4 mice per group per experiment. (**E** to **H**) Latently infected B6.WT or B6.μMt mice were transplanted with TCD-BM from CT6 mice (BALB/c NK1.1+). CD4-, CD8-, and NK1.1-depleting antibodies were administered to all groups post-transplant. (E) Viremia at day 14 post-transplant (B6.WT, n = 10; B6.μMt, n = 9) and (F) viral titers in target organs at day 16 post-transplant (B6.WT, n = 10; B6.μMt, n = 8) are shown. Data are pooled from two experiments with 3 to 5 mice per group per experiment. (G) MCMV-specific antibody titer pre-transplant was measured using a complement-dependent neutralization assay. (H) MCMV-specific IgM and IgG anti-bodies were measured by enzyme-linked immunosorbent assay at day 16 post-transplant (B6.WT, n = 5; B6.μMt, n = 3). OD, optical density. (**I** and **J**) Latently infected B6.WT or B6.μMt mice were transplanted with CT6 TCD-BM or BM + T cells and treated with CD4-, CD8-, and NK1.1-depleting antibodies post-transplant, as indicated. (I) Viremia at the indicated time points p.i. and (J) viral titers in target organs (n = 4 or 5 per time point). Data are representative of two individual experiments. (**K** and **L**) Latently infected B6D2F1 mice were transplanted with TCD-BM from B6. WT or B6.μMt mice and depleted of T cells and NK cells post-transplant. One group received B6.WT BM + T cells to induce GVHD. (K) Viremia at days 21 and 28 post-transplant and (L) viral loads in target organs at day 28 post-transplant are shown (n = 7 or 8 per time point). Data are combined from two experiments with 3 or 4 mice per group per experiment. The mean is plotted for (I) and (J). All other data represent mean ± SEM. *P < 0.05, **P < 0.01, ***P < 0.001 (Mann-Whitney U test). A dotted line represents the limit of detection.

IgM antibodies were scant or absent in both GVHD and non-GVHD mice (Fig. 3B). The neutralizing capacity of antibodies present in the serum at day 28 post-transplant was not significantly different between GVHD and non-GVHD groups (Fig. 3C). In contrast, serum isolated from mice with GVHD at day 28 post-transplant showed a complete inability to inhibit cell-to-cell spread of MCMV in vitro (table S1 and fig. S4). Thus, inhibition of cell-to-cell spread in vitro is the best indicator of protective capacity in vivo, suggesting that this is a major mechanism by which antibodies inhibit viral reactivation and spread after transplantation.

Mechanistically, antibody-mediated protection can also operate via antibody-dependent cell-mediated cytotoxicity (ADCC), which requires an interaction with Fc-receptor–expressing cells. No reactivation was observed in latently infected mice that received FcγRIII-deficient grafts and immunodepletion (Fig. 3D). Thus, the protection mediated by MCMV antibodies occurs independently of donor FcγRIII-mediated ADCC.

GVHD results in long-term cellular immunodeficiency and impaired pathogen-specific immunity (20). The B cell compartment is slow to reconstitute and B cell numbers can take several years to return to normal, leaving recipients with impaired humoral immunity (14, 21). Mature splenic B cells (Fig. 3E) and plasma cells in BM (Fig. 3F) were significantly reduced in latently infected recipients with GVHD, as compared with non-GVHD mice. Plasma cells are long-lived and reported to be radiation-resistant (22). However, plasma cell numbers were greatly reduced
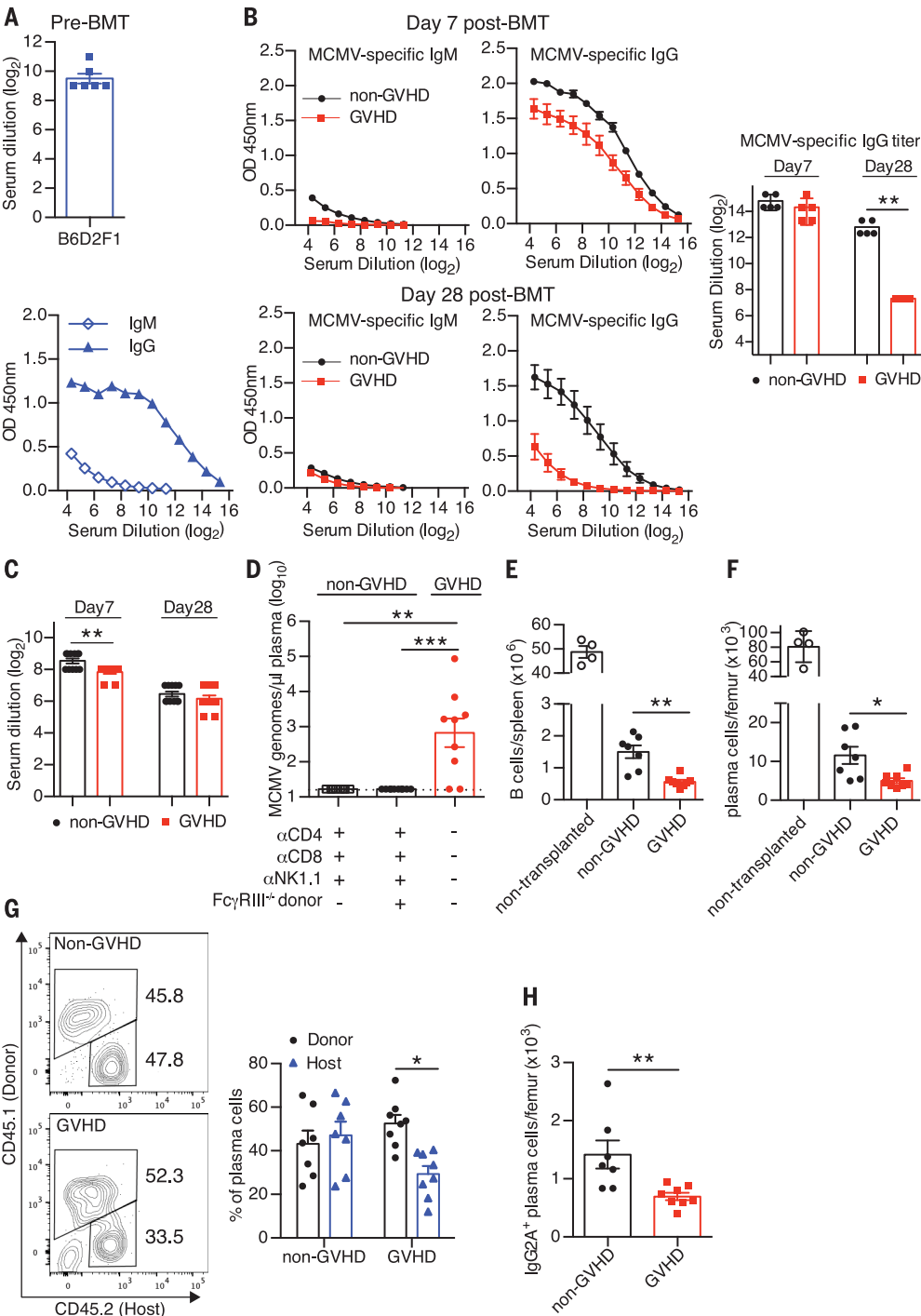

Fig. 3. MCMV reactivation in GVHD correlates with reduced levels of MCMV-specific antibodies. (**A**) MCMV-specific neutralizing antibodies (top) and MCMV-specific IgM and IgG quantification (bottom) in latently infected B6D2F1 mice pre-transplant ($n = 6$ per group) are shown. (**B** to **H**) Latently infected B6D2F1 mice were transplanted with B6 TCD-BM (non-GVHD) or BM + T cells (GVHD). (B) MCMV-specific IgM and IgG quantification at days 7 and 28 post-transplant ($n = 6$ per group) is shown. MCMV-specific IgG titers, calculated as described in the supplementary materials and methods, together with statistical analysis, are shown in the far right graph. Data are representative of two experiments where $n = 4$ mice per group. (C) Levels of neutralizing antibodies at days 7 and 28 post-transplant (non-GVHD, $n = 11$; GVHD, $n = 12$) are shown. Data are combined from two experiments with 5 or 6 mice per group per experiment. (D) Latently infected B6D2F1 hosts were transplanted with B6.WT or B6.FcγRIII$^{-/-}$, TCD-BM (non-GVHD), or BM + T cells (GVHD), and treated with the anti-CD4, -CD8, and -NK1.1 depleting antibodies, as indicated. Viremia at 4 weeks post-transplant is shown. $n > 8$ per group from two experiments with 4 or 5 mice per group per experiment. The number of (E) mature B cells in the spleen and (F) plasma cells in BM of latently infected B6D2F1 mice 14 days post-transplant (non-GVHD, $n = 7$; GVHD, $n = 8$) is shown. Data are combined from two experiments with 3 or 4 mice per group per experiment. Nontransplanted controls are shown for comparison. (G) The relative contributions of host and donor cells to the plasma cell pool are shown. (H) The number of IgG2A$^+$ plasma cells in BM is shown (non-GVHD, $n = 7$; GVHD, $n = 8$). Data are combined from two experiments with 3 or 4 mice per group per experiment. Data represent mean ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (Mann-Whitney U test).

post-transplant in both non-GVHD and GVHD recipients (Fig. 3F). The relative contribution of donor and host to the plasma cell pool in BM demonstrated that there was a significant enhancement of recipient plasma cell loss under GVHD conditions (Fig. 3G). Host IgG2A$^+$ plasma cell numbers were also reduced by GVHD (Fig. 3H). Thus, although recipient plasma cells can persist post-transplant, they are actively eliminated by the GVHD reaction.

Next, we examined whether passively acquired antibodies could limit MCMV reactivation in recipients with GVHD. The adoptive transfer of immune serum did not affect the development of GVHD (Fig. 4A), but it did protect mice from
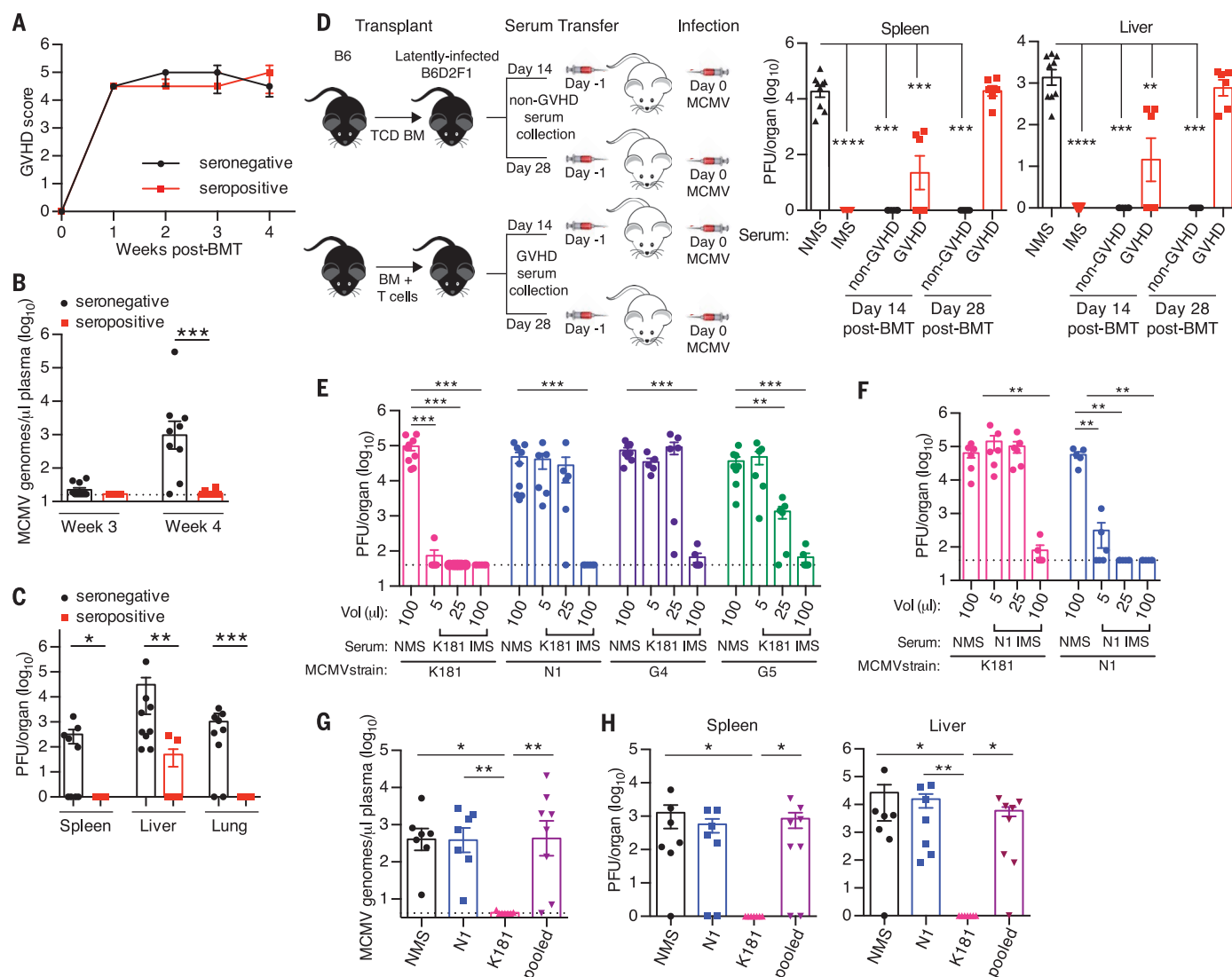
Fig. 4. Strain-specific serotherapy prevents MCMV reactivation. Latently infected B6D2F1 mice were transplanted with B6 BM + T cells. Serum from latently infected (seropositive) or uninfected (seronegative) BALB/c mice was injected twice weekly post-transplant. (**A**) GVHD scores of mice that received serum from seronegative (black) and seropositive (red) donors (median and interquartile range) are shown. (**B**) Viremia at 3 and 4 weeks post-transplant and (**C**) viral titers in organs at 4 weeks post-transplant (seronegative, $n = 9$; seropositive, $n = 10$) are shown. Data are pooled from two experiments with 4 to 6 mice per group per experiment. (**D**) Serum collected from non-GVHD or GVHD mice at day 14 or 28 post-BMT (as per schema), naïve mouse serum (NMS), or serum from latently infected mice (IMS) was injected into BALB/c 3-week-old weaners. Mice were infected with MCMV 24 hours later. Viral titers quantified 4 days p.i. are shown. Data are combined from two experiments with 3 mice per group per experiment, except for NMS and IMS, where $n = 9$ from three experiments. (**E**) NMS or immune serum collected from BALB/c mice latently infected with K181 (K181 IMS) was injected into BALB/c weaners before infection with K181, N1, G4,

or G5 viral isolates. The transferred serum volumes are indicated. Viral titers in the spleen 4 days p.i. are shown. Data are combined from two experiments with 3 to 6 mice per group per experiment. (**F**) NMS or serum collected from BALB/c mice latently infected with the N1 strain (N1 IMS) was transferred to BALB/c weaners before infection with the K181 or N1 viral strains. Viral titers in the spleen 4 days p.i. are shown. Data are combined from two experiments with 2 or 3 mice per group per experiment. (**G** and **H**) B6D2F1 mice latently infected with K181 were transplanted with B6 BM + T cells to induce GVHD. NMS or serum from mice latently infected with K181, N1, or sera pooled from mice individually infected with one of eight different MCMV isolates (including K181) was injected twice weekly from day 14 post-transplant. (G) Viremia and (H) viral titers in the indicated organs at 4 weeks post-transplant are shown. Data are combined from two experiments with 3 or 4 mice per group per experiment. Data represent mean ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ [Mann-Whitney U test used for all analyses, except for those represented in (G) and (H), where the Kruskal-Wallis H test was used].

reactivation (Fig. 4, B and C). Because MCMV antibody levels were compromised by GVHD, we investigated whether antibody present under such conditions was able to limit MCMV infection. Serum collected at days 14 and 28 post-transplant from latently infected mice, with or without GVHD, was transferred to highly susceptible 3-week-old mice (18) before primary MCMV infection (Fig. 4D). Serum from transplanted mice without GVHD limited viral replication to the same extent as treatment with immune serum (Fig. 4D and fig. S5). In contrast, serum collected from mice with GVHD showed incomplete protection, which diminished over the course of GVHD, such that serum collected at day 28 post-transplant showed no protection (Fig. 4D and fig. S5). Thus, the loss of preexisting antibodies and elimination of recipient plasma cells lead to MCMV reactivation in recipients with GVHD.

Previous attempts to ameliorate CMV disease in transplant recipients with immunoglobulins, purified from either normal donors (intravenous immunoglobulin) or donors with high CMV antibody titers (CMV-IG), have provided ambiguous results (1, 23, 24). We tested the potential requirement for virus-strain–specific antibodies in 3-week-old mice by examining whether immune serum from mice infected with MCMV-K181 afforded protection against infection with unrelated MCMV strains. As little as 5 μl of K181 immune serum provided complete protection against infection with the same viral isolate (Fig. 4E and fig. S6). In comparison, protection against infection with three unrelated MCMV isolates (N1, G4, and G5) required immune serum to be administered in significantly larger quantities (5- to 20-fold) (Fig. 4E and fig. S6). Similar findings were obtained when immune serum from mice latently infected with the N1 isolate was tested in a reverse experimental setting (Fig. 4F and fig. S7). Finally, the capacity of antibodies to protect against reactivation of an antigenically mismatched MCMV strain was tested. Treatment of transplant recipients with K181 serum prevented reactivation of K181 (Fig. 4, G and H, and fig. S8). In contrast, neither the serum that was specific for the N1 isolate nor pooled sera generated by combining serum from mice individually infected with eight different MCMV isolates (including K181) were able to prevent

K181 reactivation (Fig. 4, G and H, and fig. S8). Thus, CMV serotherapy is effective and confers high-level protection, even during GVHD, provided that the antibodies are specific for the infecting CMV isolate. Conversely, the dilution of strain-specific antibodies in polyclonal preparations renders them ineffective. This may explain the poor efficacy of polyclonal CMV immunoglobulin therapy observed in clinical studies.

The importance of strain-specific antibodies is consistent with the fact that superinfection with multiple genetic variants of HCMV is common (25). Furthermore, preexisting immunity to one HCMV strain does not inevitably confer protection against other strains (26, 27). Although significant variability in the capacity of human sera to neutralize heterologous HCMV isolates in vitro has been noted (28), strain-specific neutralization has not been extensively examined. Our study provides the basis for validation in clinical settings of HCMV infection.

The identification of potently neutralizing antibodies against a viral pentameric complex has sparked renewed interest in antibody therapy for HCMV (29–31). Thus, patient-derived serotherapy after transplant or the use of broadly neutralizing monoclonal antibodies emerge as potential strategies likely to meet the urgent need for inexpensive, nontoxic therapies to prevent and treat CMV reactivation and improve transplantation outcomes.

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Serotherapy treats a transplant hurdle

Cytomegalovirus (CMV) infection and reactivation are common and potentially fatal complications after bone marrow or hematopoietic stem cell transplantation (BMT). Martins *et al.* developed faithful preclinical murine models of CMV reactivation following BMT and found that humoral immunity can prevent this process (see the Perspective by Alegre). After BMT, antiviral antibodies that would have kept CMV at bay dwindle because host plasma cells are ablated and the donor B cell pool reconstitutes poorly. CMV reactivation was prevented by transferring antibody-containing immune serum. Such a therapeutic strategy would avoid some limitations of cellular therapies for BMT patients.

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