



Targeting Human-Cytomegalovirus-Infected Cells by Redirecting T Cells Using an Anti-CD3/Anti-Glycoprotein B Bispecific Antibody

Weixu Meng,^{a*} Aimin Tang,^b Xiaohua Ye,^a Xun Gui,^a Leike Li,^a Xuejun Fan,^a Robbie D. Schultz,^a Daniel C. Freed,^b Sha Ha,^b Dai Wang,^b Ningyan Zhang,^a Tong-Ming Fu,^b Zhiqiang An^a

^aTexas Therapeutics Institute, Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, Texas, USA

^bMerck Research Laboratories, Merck & Co., Inc., Kenilworth, New Jersey, USA

Human cytomegalovirus (HCMV) is a major cause of congenital and acquired immunodeficiency. HCMV infection can lead to severe complications in immunocompromised individuals, including organ transplantation recipients and patients with HIV/AIDS. Current treatments for HCMV infection are limited and often associated with significant toxicity. We have developed a novel therapeutic approach to target HCMV-infected cells by redirecting T cells using a bispecific antibody (BsAb) that binds to CD3 on T cells and glycoprotein B (gB) on HCMV-infected cells. This BsAb, designated as anti-CD3/gB BsAb, was shown to be highly effective in redirecting T cells to HCMV-infected cells in vitro and in vivo. In vitro, the anti-CD3/gB BsAb significantly increased the cytotoxicity of T cells against HCMV-infected cells, leading to a reduction in viral titers. In vivo, the anti-CD3/gB BsAb was shown to be effective in reducing viral titers in a murine model of HCMV infection. These results suggest that the anti-CD3/gB BsAb may be a promising therapeutic agent for the treatment of HCMV infection.

Keywords: Human cytomegalovirus (HCMV), T cells, bispecific antibody (BsAb), redirection, cytotoxicity.

Human cytomegalovirus (HCMV) is a major cause of congenital and acquired immunodeficiency. HCMV infection can lead to severe complications in immunocompromised individuals, including organ transplantation recipients and patients with HIV/AIDS. Current treatments for HCMV infection are limited and often associated with significant toxicity. We have developed a novel therapeutic approach to target HCMV-infected cells by redirecting T cells using a bispecific antibody (BsAb) that binds to CD3 on T cells and glycoprotein B (gB) on HCMV-infected cells. This BsAb, designated as anti-CD3/gB BsAb, was shown to be highly effective in redirecting T cells to HCMV-infected cells in vitro and in vivo. In vitro, the anti-CD3/gB BsAb significantly increased the cytotoxicity of T cells against HCMV-infected cells, leading to a reduction in viral titers. In vivo, the anti-CD3/gB BsAb was shown to be effective in reducing viral titers in a murine model of HCMV infection. These results suggest that the anti-CD3/gB BsAb may be a promising therapeutic agent for the treatment of HCMV infection.

Human cytomegalovirus (HCMV) is a major cause of congenital and acquired immunodeficiency. HCMV infection can lead to severe complications in immunocompromised individuals, including organ transplantation recipients and patients with HIV/AIDS. Current treatments for HCMV infection are limited and often associated with significant toxicity. We have developed a novel therapeutic approach to target HCMV-infected cells by redirecting T cells using a bispecific antibody (BsAb) that binds to CD3 on T cells and glycoprotein B (gB) on HCMV-infected cells. This BsAb, designated as anti-CD3/gB BsAb, was shown to be highly effective in redirecting T cells to HCMV-infected cells in vitro and in vivo. In vitro, the anti-CD3/gB BsAb significantly increased the cytotoxicity of T cells against HCMV-infected cells, leading to a reduction in viral titers. In vivo, the anti-CD3/gB BsAb was shown to be effective in reducing viral titers in a murine model of HCMV infection. These results suggest that the anti-CD3/gB BsAb may be a promising therapeutic agent for the treatment of HCMV infection.

Received 18 August 2017 Returned for modification 7 September 2017 Accepted 10 October 2017

Accepted manuscript posted online 16 October 2017

Citation Meng W, Tang A, Ye X, Gui X, Li L, Fan X, Schultz RD, Freed DC, Ha S, Wang D, Zhang N, Fu T-M, An Z. 2018. Targeting human-cytomegalovirus-infected cells by redirecting T cells using an anti-CD3/anti-glycoprotein B bispecific antibody. *Antimicrob Agents Chemother* 62:e01719-17. <https://doi.org/10.1128/AAC.01719-17>.

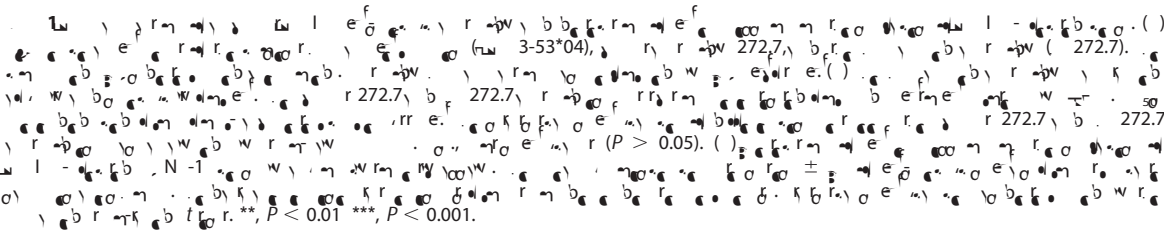
Copyright © 2017 Meng et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/).

Address correspondence to Tong-Ming Fu, tong-ming_fu@merck.com, or Zhiqiang An, Zhiqiang.An@uth.tmc.edu.

* Present address: Weixu Meng, Division of Hematopoietic Stem Cell and Leukemia Research, Gehl Family Center for Leukemia Research, City of Hope, Duarte, California, USA.

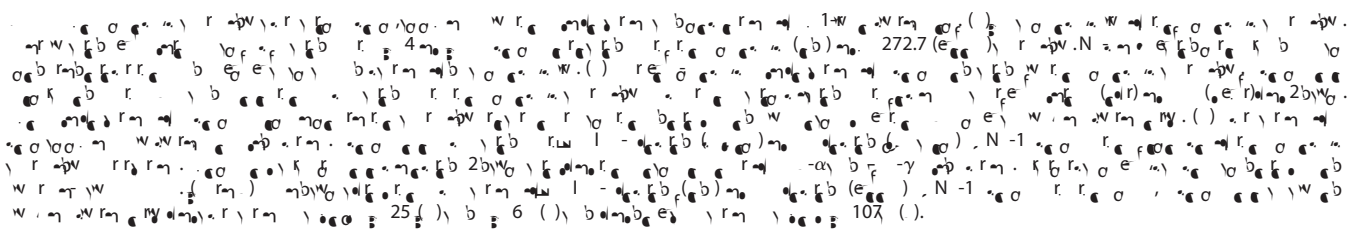
ר₁ e_f r₂ b₁ e_f r₃ w₁ (3,4). ר₁ e_f r₂ b₁ e_f r₃ w₁ e_f r₄ b₂ e_f r₅ w₂ e_f r₆ b₃ e_f r₇ w₃ e_f r₈ b₄ e_f r₉ w₄ e_f r₁₀ b₅ e_f r₁₁ w₅ e_f r₁₂ b₆ e_f r₁₃ w₆ e_f r₁₄ b₇ e_f r₁₅ w₇ e_f r₁₆ b₈ e_f r₁₇ w₈ e_f r₁₈ b₉ e_f r₁₉ w₉ e_f r₂₀ b₁₀ e_f r₂₁ w₁₀ e_f r₂₂ b₁₁ e_f r₂₃ w₁₁ e_f r₂₄ b₁₂ e_f r₂₅ w₁₂ e_f r₂₆ b₁₃ e_f r₂₇ w₁₃ e_f r₂₈ b₁₄ e_f r₂₉ w₁₄ e_f r₃₀ b₁₅ e_f r₃₁ w₁₅ e_f r₃₂ b₁₆ e_f r₃₃ w₁₆ e_f r₃₄ b₁₇ e_f r₃₅ w₁₇ e_f r₃₆ b₁₈ e_f r₃₇ w₁₈ e_f r₃₈ b₁₉ e_f r₃₉ w₁₉ e_f r₄₀ b₂₀ e_f r₄₁ w₂₀ e_f r₄₂ b₂₁ e_f r₄₃ w₂₁ e_f r₄₄ b₂₂ e_f r₄₅ w₂₂ e_f r₄₆ b₂₃ e_f r₄₇ w₂₃ e_f r₄₈ b₂₄ e_f r₄₉ w₂₄ e_f r₅₀ b₂₅ e_f r₅₁ w₂₅ e_f r₅₂ b₂₆ e_f r₅₃ w₂₆ e_f r₅₄ b₂₇ e_f r₅₅ w₂₇ e_f r₅₆ b₂₈ e_f r₅₇ w₂₈ e_f r₅₈ b₂₉ e_f r₅₉ w₂₉ e_f r₆₀ b₃₀ e_f r₆₁ w₃₀ e_f r₆₂ b₃₁ e_f r₆₃ w₃₁ e_f r₆₄ b₃₂ e_f r₆₅ w₃₂ e_f r₆₆ b₃₃ e_f r₆₇ w₃₃ e_f r₆₈ b₃₄ e_f r₆₉ w₃₄ e_f r₇₀ b₃₅ e_f r₇₁ w₃₅ e_f r₇₂ b₃₆ e_f r₇₃ w₃₆ e_f r₇₄ b₃₇ e_f r₇₅ w₃₇ e_f r₇₆ b₃₈ e_f r₇₇ w₃₈ e_f r₇₈ b₃₉ e_f r₇₉ w₃₉ e_f r₈₀ b₄₀ e_f r₈₁ w₄₀ e_f r₈₂ b₄₁ e_f r₈₃ w₄₁ e_f r₈₄ b₄₂ e_f r₈₅ w₄₂ e_f r₈₆ b₄₃ e_f r₈₇ w₄₃ e_f r₈₈ b₄₄ e_f r₈₉ w₄₄ e_f r₉₀ b₄₅ e_f r₉₁ w₄₅ e_f r₉₂ b₄₆ e_f r₉₃ w₄₆ e_f r₉₄ b₄₇ e_f r₉₅ w₄₇ e_f r₉₆ b₄₈ e_f r₉₇ w₄₈ e_f r₉₈ b₄₉ e_f r₉₉ w₄₉ e_f r₁₀₀ b₅₀ e_f r₁₀₁ w₅₀ e_f r₁₀₂ b₅₁ e_f r₁₀₃ w₅₁ e_f r₁₀₄ b₅₂ e_f r₁₀₅ w₅₂ e_f r₁₀₆ b₅₃ e_f r₁₀₇ w₅₃ e_f r₁₀₈ b₅₄ e_f r₁₀₉ w₅₄ e_f r₁₁₀ b₅₅ e_f r₁₁₁ w₅₅ e_f r₁₁₂ b₅₆ e_f r₁₁₃ w₅₆ e_f r₁₁₄ b₅₇ e_f r₁₁₅ w₅₇ e_f r₁₁₆ b₅₈ e_f r₁₁₇ w₅₈ e_f r₁₁₈ b₅₉ e_f r₁₁₉ w₅₉ e_f r₁₂₀ b₆₀ e_f r₁₂₁ w₆₀ e_f r₁₂₂ b₆₁ e_f r₁₂₃ w₆₁ e_f r₁₂₄ b₆₂ e_f r₁₂₅ w₆₂ e_f r₁₂₆ b₆₃ e_f r₁₂₇ w₆₃ e_f r₁₂₈ b₆₄ e_f r₁₂₉ w₆₄ e_f r₁₃₀ b₆₅ e_f r₁₃₁ w₆₅ e_f r₁₃₂ b₆₆ e_f r₁₃₃ w₆₆ e_f r₁₃₄ b₆₇ e_f r₁₃₅ w₆₇ e_f r₁₃₆ b₆₈ e_f r₁₃₇ w₆₈ e_f r₁₃₈ b₆₉ e_f r₁₃₉ w₆₉ e_f r₁₄₀ b₇₀ e_f r₁₄₁ w₇₀ e_f r₁₄₂ b₇₁ e_f r₁₄₃ w₇₁ e_f r₁₄₄ b₇₂ e_f r₁₄₅ w₇₂ e_f r₁₄₆ b₇₃ e_f r₁₄₇ w₇₃ e_f r₁₄₈ b₇₄ e_f r₁₄₉ w₇₄ e_f r₁₅₀ b₇₅ e_f r₁₅₁ w₇₅ e_f r₁₅₂ b₇₆ e_f r₁₅₃ w₇₆ e_f r₁₅₄ b₇₇ e_f r₁₅₅ w₇₇ e_f r₁₅₆ b₇₈ e_f r₁₅₇ w₇₈ e_f r₁₅₈ b₇₉ e_f r₁₅₉ w₇₉ e_f r₁₆₀ b₈₀ e_f r₁₆₁ w₈₀ e_f r₁₆₂ b₈₁ e_f r₁₆₃ w₈₁ e_f r₁₆₄ b₈₂ e_f r₁₆₅ w₈₂ e_f r₁₆₆ b₈₃ e_f r₁₆₇ w₈₃ e_f r₁₆₈ b₈₄ e_f r₁₆₉ w₈₄ e_f r₁₇₀ b₈₅ e_f r₁₇₁ w₈₅ e_f r₁₇₂ b₈₆ e_f r₁₇₃ w₈₆ e_f r₁₇₄ b₈₇ e_f r₁₇₅ w₈₇ e_f r₁₇₆ b₈₈ e_f r₁₇₇ w₈₈ e_f r₁₇₈ b₈₉ e_f r₁₇₉ w₈₉ e_f r₁₈₀ b₉₀ e_f r₁₈₁ w₉₀ e_f r₁₈₂ b₉₁ e_f r₁₈₃ w₉₁ e_f r₁₈₄ b₉₂ e_f r₁₈₅ w₉₂ e_f r₁₈₆ b₉₃ e_f r₁₈₇ w₉₃ e_f r₁₈₈ b₉₄ e_f r₁₈₉ w₉₄ e_f r₁₉₀ b₉₅ e_f r₁₉₁ w₉₅ e_f r₁₉₂ b₉₆ e_f r₁₉₃ w₉₆ e_f r₁₉₄ b₉₇ e_f r₁₉₅ w₉₇ e_f r₁₉₆ b₉₈ e_f r₁₉₇ w₉₈ e_f r₁₉₈ b₉₉ e_f r₁₉₉ w₉₉ e_f r₂₀₀ b₁₀₀ e_f r₂₀₁ w₁₀₀ e_f r₂₀₂ b₁₀₁ e_f r₂₀₃ w₁₀₁ e_f r₂₀₄ b₁₀₂ e_f r₂₀₅ w₁₀₂ e_f r₂₀₆ b₁₀₃ e_f r₂₀₇ w₁₀₃ e_f r₂₀₈ b₁₀₄ e_f r₂₀₉ w₁₀₄ e_f r₂₁₀ b₁₀₅ e_f r₂₁₁ w₁₀₅ e_f r₂₁₂ b₁₀₆ e_f r₂₁₃ w₁₀₆ e_f r₂₁₄ b₁₀₇ e_f r₂₁₅ w₁₀₇ e_f r₂₁₆ b₁₀₈ e_f r₂₁₇ w₁₀₈ e_f r₂₁₈ b₁₀₉ e_f r₂₁₉ w₁₀₉ e_f r₂₂₀ b₁₁₀ e_f r₂₂₁ w₁₁₀ e_f r₂₂₂ b₁₁₁ e_f r₂₂₃ w₁₁₁ e_f r₂₂₄ b₁₁₂ e_f r₂₂₅ w₁₁₂ e_f r₂₂₆ b₁₁₃ e_f r₂₂₇ w₁₁₃ e_f r₂₂₈ b₁₁₄ e_f r₂₂₉ w₁₁₄ e_f r₂₃₀ b₁₁₅ e_f r₂₃₁ w₁₁₅ e_f r₂₃₂ b₁₁₆ e_f r₂₃₃ w₁₁₆ e_f r₂₃₄ b₁₁₇ e_f r₂₃₅ w₁₁₇ e_f r₂₃₆ b₁₁₈ e_f r₂₃₇ w₁₁₈ e_f r₂₃₈ b₁₁₉ e_f r₂₃₉ w₁₁₉ e_f r₂₄₀ b₁₂₀ e_f r₂₄₁ w₁₂₀ e_f r₂₄₂ b₁₂₁ e_f r₂₄₃ w₁₂₁ e_f r₂₄₄ b₁₂₂ e_f r₂₄₅ w₁₂₂ e_f r₂₄₆ b₁₂₃ e_f r₂₄₇ w₁₂₃ e_f r₂₄₈ b₁₂₄ e_f r₂₄₉ w₁₂₄ e_f r₂₅₀ b₁₂₅ e_f r₂₅₁ w₁₂₅ e_f r₂₅₂ b₁₂₆ e_f r₂₅₃ w₁₂₆ e_f r₂₅₄ b₁₂₇ e_f r₂₅₅ w₁₂₇ e_f r₂₅₆ b₁₂₈ e_f r₂₅₇ w₁₂₈ e_f r₂₅₈ b₁₂₉ e_f r₂₅₉ w₁₂₉ e_f r₂₆₀ b₁₃₀ e_f r₂₆₁ w₁₃₀ e_f r₂₆₂ b₁₃₁ e_f r₂₆₃ w₁₃₁ e_f r₂₆₄ b₁₃₂ e_f r₂₆₅ w₁₃₂ e_f r₂₆₆ b₁₃₃ e_f r₂₆₇ w₁₃₃ e_f r₂₆₈ b₁₃₄ e_f r₂₆₉ w₁₃₄ e_f r₂₇₀ b₁₃₅ e_f r₂₇₁ w₁₃₅ e_f r₂₇₂ b₁₃₆ e_f r₂₇₃ w₁₃₆ e_f r₂₇₄ b₁₃₇ e_f r₂₇₅ w₁₃₇ e_f r₂₇₆ b₁₃₈ e_f r₂₇₇ w₁₃₈ e_f r₂₇₈ b₁₃₉ e_f r₂₇₉ w₁₃₉ e_f r₂₈₀ b₁₄₀ e_f r₂₈₁ w₁₄₀ e_f r₂₈₂ b₁₄₁ e_f r₂₈₃ w₁₄₁ e_f r₂₈₄ b₁₄₂ e_f r₂₈₅ w₁₄₂ e_f r₂₈₆ b₁₄₃ e_f r₂₈₇ w₁₄₃ e_f r₂₈₈ b₁₄₄ e_f r₂₈₉ w₁₄₄ e_f r₂₉₀ b₁₄₅ e_f r₂₉₁ w₁₄₅ e_f r₂₉₂ b₁₄₆ e_f r₂₉₃ w₁₄₆ e_f r₂₉₄ b₁₄₇ e_f r₂₉₅ w₁₄₇ e_f r₂₉₆ b₁₄₈ e_f r₂₉₇ w₁₄₈ e_f r₂₉₈ b₁₄₉ e_f r₂₉₉ w₁₄₉ e_f r₃₀₀ b₁₅₀ e_f r₃₀₁ w₁₅₀ e_f r₃₀₂ b₁₅₁ e_f r₃₀₃ w₁₅₁ e_f r₃₀₄ b₁₅₂ e_f r₃₀₅ w₁₅₂ e_f r₃₀₆ b₁₅₃ e_f r₃₀₇ w₁₅₃ e_f r₃₀₈ b₁₅₄ e_f r₃₀₉ w₁₅₄ e_f r₃₁₀ b₁₅₅ e_f r₃₁₁ w₁₅₅ e_f r₃₁₂ b₁₅₆ e_f r₃₁₃ w₁₅₆ e_f r₃₁₄ b₁₅₇ e_f r₃₁₅ w₁₅₇ e_f r₃₁₆ b₁₅₈ e_f r₃₁₇ w₁₅₈ e_f r₃₁₈ b₁₅₉ e_f r₃₁₉ w₁₅₉ e_f r₃₂₀ b₁₆₀ e_f r₃₂₁ w₁₆₀ e_f r₃₂₂ b₁₆₁ e_f r₃₂₃ w₁₆₁ e_f r₃₂₄ b₁₆₂ e_f r₃₂₅ w₁₆₂ e_f r₃₂₆ b₁₆₃ e_f r₃₂₇ w₁₆₃ e_f r₃₂₈ b₁₆₄ e_f r₃₂₉ w₁₆₄ e_f r₃₃₀ b₁₆₅ e_f r₃₃₁ w₁₆₅ e_f r₃₃₂ b₁₆₆ e_f r₃₃₃ w₁₆₆ e_f r₃₃₄ b₁₆₇ e_f r₃₃₅ w₁₆₇ e_f r₃₃₆ b₁₆₈ e_f r₃₃₇ w₁₆₈ e_f r₃₃₈ b₁₆₉ e_f r₃₃₉ w₁₆₉ e_f r₃₄₀ b₁₇₀ e_f r₃₄₁ w₁₇₀ e_f r₃₄₂ b₁₇₁ e_f r₃₄₃ w₁₇₁ e_f r₃₄₄ b₁₇₂ e_f r₃₄₅ w₁₇₂ e_f r₃₄₆ b₁₇₃ e_f r₃₄₇ w₁₇₃ e_f r₃₄₈ b₁₇₄ e_f r₃₄₉ w₁₇₄ e_f r₃₅₀ b₁₇₅ e_f r₃₅₁ w₁₇₅ e_f r₃₅₂ b₁₇₆ e_f r₃₅₃ w₁₇₆ e_f r₃₅₄ b₁₇₇ e_f r₃₅₅ w₁₇₇ e_f r₃₅₆ b₁₇₈ e_f r₃₅₇ w₁₇₈ e_f r₃₅₈ b₁₇₉ e_f r₃₅₉ w₁₇₉ e_f r₃₆₀ b₁₈₀ e_f r₃₆₁ w₁₈₀ e_f r₃₆₂ b₁₈₁ e_f r₃₆₃ w₁₈₁ e_f r₃₆₄ b₁₈₂ e_f r₃₆₅ w₁₈₂ e_f r₃₆₆ b₁₈₃ e_f r₃₆₇ w₁₈₃ e_f r₃₆₈ b₁₈₄ e_f r₃₆₉ w₁₈₄ e_f r₃₇₀ b₁₈₅ e_f r₃₇₁ w₁₈₅ e_f r₃₇₂ b₁₈₆ e_f r₃₇₃ w₁₈₆ e_f r₃₇₄ b₁₈₇ e_f r₃₇₅ w₁₈₇ e_f r₃₇₆ b₁₈₈ e_f r₃₇₇ w₁₈₈ e_f r₃₇₈ b₁₈₉ e_f r₃₇₉ w₁₈₉ e_f r₃₈₀ b₁₉₀ e_f r₃₈₁ w₁₉₀ e_f r₃₈₂ b₁₉₁ e_f r₃₈₃ w₁₉₁ e_f r₃₈₄ b₁₉₂ e_f r₃₈₅ w₁₉₂ e_f r₃₈₆ b₁₉₃ e_f r₃₈₇ w₁₉₃ e_f r₃₈₈ b₁₉₄ e_f r₃₈₉ w₁₉₄ e_f r₃₉₀ b₁₉₅ e_f r₃₉₁ w₁₉₅ e_f r₃₉₂ b₁₉₆ e_f r₃₉₃ w₁₉₆ e_f r₃₉₄ b₁₉₇ e_f r₃₉₅ w₁₉₇ e_f r₃₉₆ b₁₉₈ e_f r₃₉₇ w₁₉₈ e_f r₃₉₈ b₁₉₉ e_f r₃₉₉ w₁₉₉ e_f r₄₀₀ b₂₀₀ e_f r₄₀₁ w₂₀₀ e_f r₄₀₂ b₂₀₁ e_f r₄₀₃ w₂₀₁ e_f r₄₀₄ b₂₀₂ e_f r₄₀₅ w₂₀₂ e_f r₄₀₆ b₂₀₃ e_f r₄₀₇ w₂₀₃ e_f r₄₀₈ b₂₀₄ e_f r₄₀₉ w₂₀₄ e_f r₄₁₀ b₂₀₅ e_f r₄₁₁ w₂₀₅ e_f r₄₁₂ b₂₀₆ e_f r₄₁₃ w₂₀₆ e_f r₄₁₄ b₂₀₇ e_f r₄₁₅ w₂₀₇ e_f r₄₁₆ b₂₀₈ e_f r₄₁₇ w₂₀₈ e_f r₄₁₈ b₂₀₉ e_f r₄₁₉ w₂₀₉ e_f r₄₂₀ b₂₁₀ e_f r₄₂₁ w₂₁₀ e_f r₄₂₂ b₂₁₁ e_f r₄₂₃ w₂₁₁ e_f r₄₂₄ b₂₁₂ e_f r₄₂₅ w₂₁₂ e_f r₄₂₆ b₂₁₃ e_f r₄₂₇ w₂₁₃ e_f r₄₂₈ b₂₁₄ e_f r₄₂₉ w₂₁₄ e_f r₄₃₀ b₂₁₅ e_f r₄₃₁ w₂₁₅ e_f r₄₃₂ b₂₁₆ e_f r₄₃₃ w₂₁₆ e_f r₄₃₄ b₂₁₇ e_f r₄₃₅ w₂₁₇ e_f r₄₃₆ b₂₁₈ e_f r₄₃₇ w₂₁₈ e_f r₄₃₈ b₂₁₉ e_f r₄₃₉ w₂₁₉ e_f r₄₄₀ b₂₂₀ e_f r₄₄₁ w₂₂₀ e_f r₄₄₂ b₂₂₁ e_f r₄₄₃ w₂₂₁ e_f r₄₄₄ b₂₂₂ e_f r₄₄₅ w₂₂₂ e_f r₄₄₆ b₂₂₃ e_f r₄₄₇ w₂₂₃ e_f r₄₄₈ b₂₂₄ e_f r₄₄₉ w₂₂₄ e_f r₄₅₀ b₂₂₅ e_f r₄₅₁ w₂₂₅ e_f r₄₅₂ b₂₂₆ e_f r₄₅₃ w₂₂₆ e_f r₄₅₄ b₂₂₇ e_f r₄₅₅ w₂₂₇ e_f r₄₅₆ b₂₂₈ e_f r₄₅₇ w₂₂₈ e_f r₄₅₈ b₂₂₉ e_f r₄₅₉ w₂₂₉ e_f r₄₆₀ b₂₃₀ e_f r₄₆₁ w₂₃₀ e_f r₄₆₂ b₂₃₁ e_f r₄₆₃ w_{231</}

r . m) e^f g) b . r . d w



201 62 1 0171 -17

r . m) e^f d) b . c m . d w

[illegible]

