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Humanized mouse G6 anti-idiotypic monoclonal antibody has therapeutic potential against *IGHV169* germline gene based B-CLL

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In 10-20% of the cases of chronic lymphocytic leukemia of B-cell phenotype (B-CLL), the *IGHV169* germline is utilized as VH gene of the B-cell receptor (BCR). Mouse G6 (MuG6) is an anti-idiotypic monoclonal antibody discovered in a screen against rheumatoid factors (RFs) that binds with high affinity to an idiotope expressed on the 51p1 alleles of *IGHV169* germline gene encoded antibodies (G6-id+). The finding that unmutated *IGHV169* encoded BCRs are frequently expressed on BCLL cells provides an opportunity for antiidiotype monoclonal antibody immunotherapy. In this study, we first showed that MuG6 can deplete B-cells encoding IGHV1-69 BCRs using a novel humanized GTL mouse model. Next, we humanized MuG6 and demonstrated that the humanized antibodies (HuG6s), especially HuG6.3, displayed ~2fold higher binding affinity for G6id+ antibody compared to the parental MuG6. Additional studies showed that HuG6.3 was able to kill G6id+ BCR expressing cells and patient BCLL cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Finally, both MuG6 and HuG6.3 mediate in vivo depletion of B-CLL cells in NSG mice. These data suggest that HuG6.3 may provide a new precision medicine to selectively kill *IGHV169* encoding G6id+ BCLL cells.

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Therapeutic monoclonal antibodies: What headache specialists need to know?

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Monoclonal antibodies (mAbs) are now an important part of the treatment armamentarium for a wide range of conditions including cancer, autoimmune diseases, inflammatory diseases of the joint and bowel, transplant rejection and multiple sclerosis. Significant progress over the last 30 years in the development of therapeutic mAbs has resulted in improved efficacy and safety. Monoclonal antibodies approved for the treatment of neurological illnesses so far are limited to use in multiple sclerosis. Several therapeutic mAbs have completed phase 2 clinical trials for migraine prevention and there are phase 3 trials underway for migraine prophylaxis and for cluster headache at the time of this writing. The purpose of this review is to discuss the characteristics of mAbs, including their mechanism of action and safety profile and briefly describe the mAbs being evaluated for the prevention of migraine and cluster headaches. Monoclonal antibodies have several features that distinguish them from small molecules, including very high selectivity, relatively long half-life that generally allows for once or twice monthly dosing and significantly reduced potential for drug-drug interactions or other non target related toxicities. The clinical development of mAbs that target calcitonin gene-related peptide and its receptor is underway and will evaluate this promising new drug class for the prevention of migraine and cluster headache.

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