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Comments

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Isolation of Human Antigen-Specific Antibodies from Memory B-Cells Nearly Two Years Post Vaccination

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Abstract:

Isolation and production of therapeutic human monoclonal antibodies (mAbs) traditionally utilizes a handful of techniques including antibody engineering, phage display, hybridoma generation from transgenic mice or EBV immortalization of B-cells. Over the past decade a new approach has emerged that attempts to extract antigen-specific memory B-cells from the peripheral blood of individuals vaccinated or infected with the target. Initial attempts focused on culturing B-cells and inducing differentiation to plasmablasts for analysis of antibody-antigen specificity, but results were largely mixed due to difficult culture conditions and/or rarity of target cells. With advancing technology in cell sorting, single antigen-specific memory B-cells can be identified and sorted with fluorescently labeled antigens. This method has produced virus-specific mAbs from HIV-infected patients and tetanus-specific mAbs within weeks after Tdap immunization. Many other studies claim to have found antigen-specific mAbs months to years after immunization or clearance of an infection; however, these studies fail to provide direct evidence of antibody specificity by cloning and expressing the mAbs from B-cells.

Here we report the efficient isolation of tetanus-specific mAbs from a subject Td-immunized almost two years prior to blood draw. Initially, the total B-cell population was isolated from peripheral blood mononuclear cells enriched by negative selection, then stained to identify tetanus-specific memory B-cells. These cells were individually sorted and PCR was performed to amplify heavy and light chain variable regions of the B-cell's antibody mRNA. After sequencing, 15 of 42 samples produced both heavy and light chain antibody sequence and 11 mAbs were cloned and transiently expressed. ELISA analysis indicated 5 of the 11 mAbs bound the Hc protein fragment of tetanus toxin and 3 were specific for Hc. We plan to extend this initial success to additional targets and longer gaps between vaccination and B-cell isolation to identify functional therapeutic human antibodies.