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Peptide Mimetics for Therapeutic Dose Monitoring of Monoclonal Antibodies

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PURPOSE

Monoclonal antibodies (mAb) are among the most rapidly growing class of pharmaceuticals as well as the most costly. The pharmacokinetic variation among patients treated with these agents is significant, typically varying by more than two orders of magnitude. This variation can be compounded by the development of anti-drug antibodies as therapy continues. Furthermore, several studies with different mAb have suggested correlation between circulating mAb levels and therapeutic outcome and adverse effects. Thus, knowledge of a patient's actual drug levels during treatment is critical for optimizing therapeutic responses and minimizing unnecessary side effects. However, therapeutic dose monitoring is not routine practice in part to due to the paucity of robust clinical lab or point-of-care assay solutions. We describe here an innovative approach based on peptide mimetics for rapid, simple, and sensitive therapeutic dose monitoring of mAb therapeutics both during clinical development and after market approval.

METHOD

Phage displayed peptide libraries are used to select peptide sequences that mimic the target antigen of a given mAb. The selected peptides invariably bind to the antigen-binding site of the antibody and are competed by the natural ligand. Biotinylated synthetic peptides are attached to streptavidin coated solid phases and used as a ligand for capture of the cognate mAb in ELISA. The peptides are also incorporated into lateral flow immunoassays for rapid, lab-free analysis.

RESULTS

We have developed mimetope peptides against a broad range of therapeutic mAb. When used as a capture reagent in ELISAs, these mimetope peptides display sufficient sensitivity, specificity, and linearity across the requisite concentration ranges relevant for most mAb pharmacokinetics studies. In addition to ELISAs suitable for rituximab and alemtuzumab detection, we have also developed assays for trastuzumab, ipilimumab, obinutuzumab, and natalizumab quantitation in biological samples. Importantly, the selected peptides bind only to their cognate mAb and do not crossreact with other mAb or native IgG.

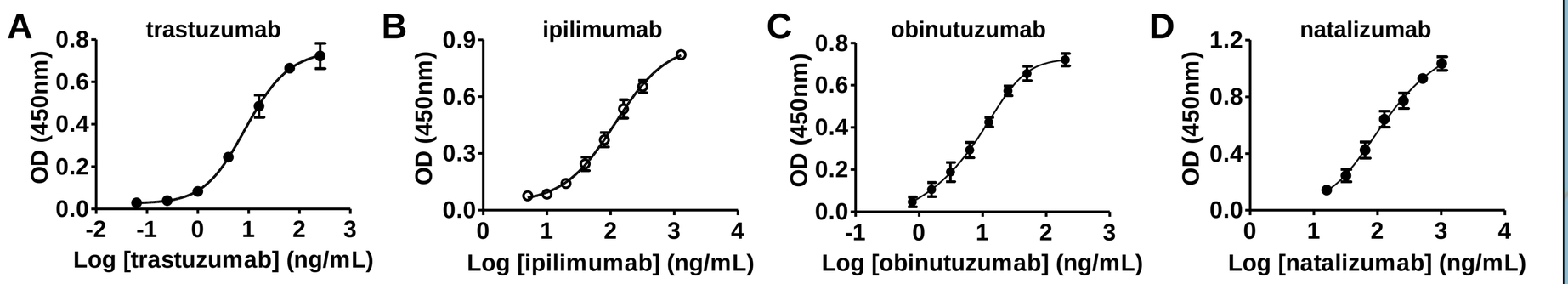

Figure 1. Calibration Curves of Mimetope-based ELISA Specific for Trastuzumab, Ipilimumab, Obinutuzumab and Natalizumab. A) The calibration range of the trastuzumab assay is of 5-20ng/mL after applying the minimum required sample dilution of 1/1000, corresponding to 5-20ug/mL trastuzumab in undiluted serum. B) The ipilimumab assay has a dynamic range of 25-160ng/mL after sample dilution, which corresponds to 12.5 – 80ug/mL range of ipilimumab in undiluted serum. C) The assay designed to measure obinutuzumab as a dynamic range 3-30ng/mL after sample dilution, corresponding to 3-30ug/mL in undiluted plasma. D) The natalizumab assay has a calibration range from 16 to 256ng/mL after sample dilution, which corresponds to 4-64ug/mL in undiluted serum.

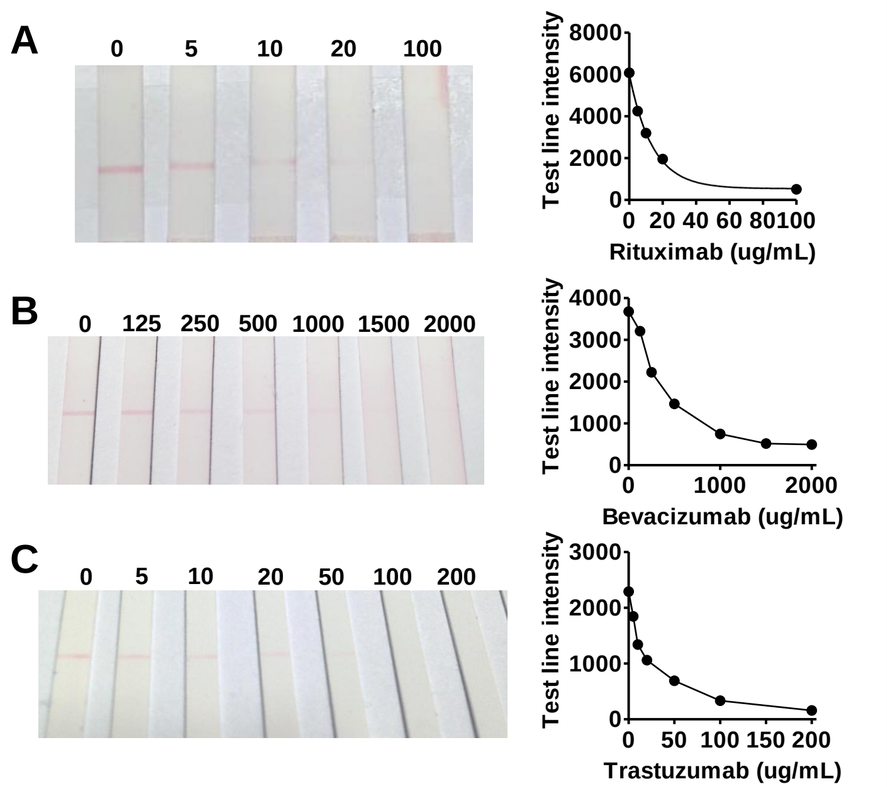

Figure 2. Lateral Flow Immunoassay (LFA) using Mimetope Peptides for Therapeutic Dose Monitoring. Prototype competitive LFA have been developed for quantitative measurement of rituximab (A), bevacizumab (B), and trastuzumab (C) in human serum samples, with dynamic ranges of 0-100 ug/mL, 0-2000 ug/mL, and 0-200 ug/mL respectively. The quantitative potential of this competitive LFA approach was established by spiking the drug of interest into human serum and measuring test line intensity with a LFA reader 5 minutes after sample application.

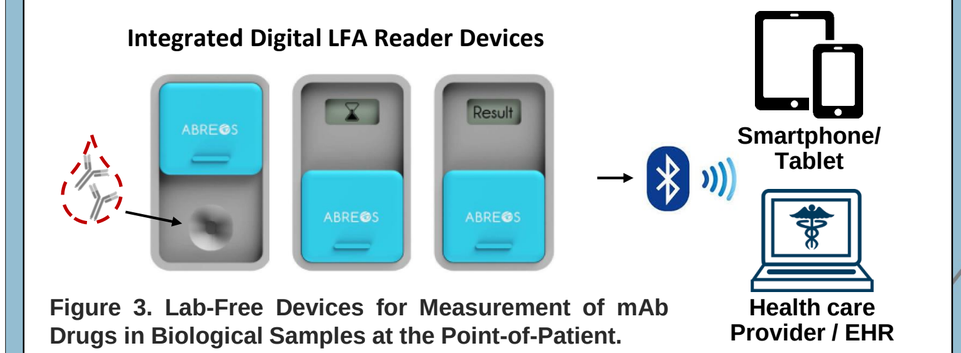

Figure 3. Lab-Free Devices for Measurement of mAb Drugs in Biological Samples at the Point-of-Patient.

CONCLUSION

Peptide mimetic ligands are an attractive option for immunoassay reagents because they are stable, specific, inexpensive, and adaptable to most immunoassay formats, including ELISA and LFA. Peptide mimics are particularly advantageous when the target is a cell surface antigen, which is both challenging and expensive to produce in soluble form. We are currently developing quantitative integrated digital reader devices for therapeutic dose monitoring in point-of-care settings and validating the assays in clinical studies.

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