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DEVELOPING AN FDA-QUALIFIED DRUG DEVELOPMENT TOOL, THE MEMBRANE PROTEOME ARRAY, FOR SPECIFICITY TESTING OF ANTIBODIES AND CAR-T CELL THERAPIES

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Background Detailed specificity of antibody-based therapies, including CAR-T cells, is required for preclinical safety assessment and IND submissions to the FDA. The FDA has established pathways to qualify Drug Development Tools through various mechanisms that now include the Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program.

Methods We developed the Membrane Proteome Array platform consisting of over 6,000 proteins expressed in live cells. The MPA assesses binding interactions by high-throughput flow cytometry, allowing for high sensitivity detection and rapid analysis. All targets identified on the MPA screen are validated by secondary titration analysis. Proteins in the MPA exist in their native conformations and are not altered by fixation. The MPA was proposed for inclusion into the IStand pilot program.

Results The MPA has been used to test the specificity and potential off-target binding liabilities for over a thousand therapeutic molecules to date, and data from MPA studies have been accepted by the FDA as a part of IND applications for antibody-based therapies. While using the MPA, we have found that approximately 25% of molecules screened display cross-reactivity. Tissue cross-reactivity (TCR) studies have been traditionally used to screen for off-target binding; however, their predictive value for in vivo safety and toxicity is poor. In contrast, we will present MPA data that precisely reveals the identity of off-target binding partners. The MPA is the first tool to have its Letter of Intent accepted into the IStand program. Here, we will provide details on the steps we have undertaken to develop the MPA as a qualified assay and describe the MPA's current status for consideration as a qualified Drug Development Tool.

Conclusions MPA data have been used in numerous successful regulatory applications for antibody-based biotherapeutics and may be used to replace or complement other cross-reactivity studies. The MPA is currently under consideration for qualification by FDA's IStand program.

<http://dx.doi.org/10.1136/jitc-2023-SITC2023.1431>