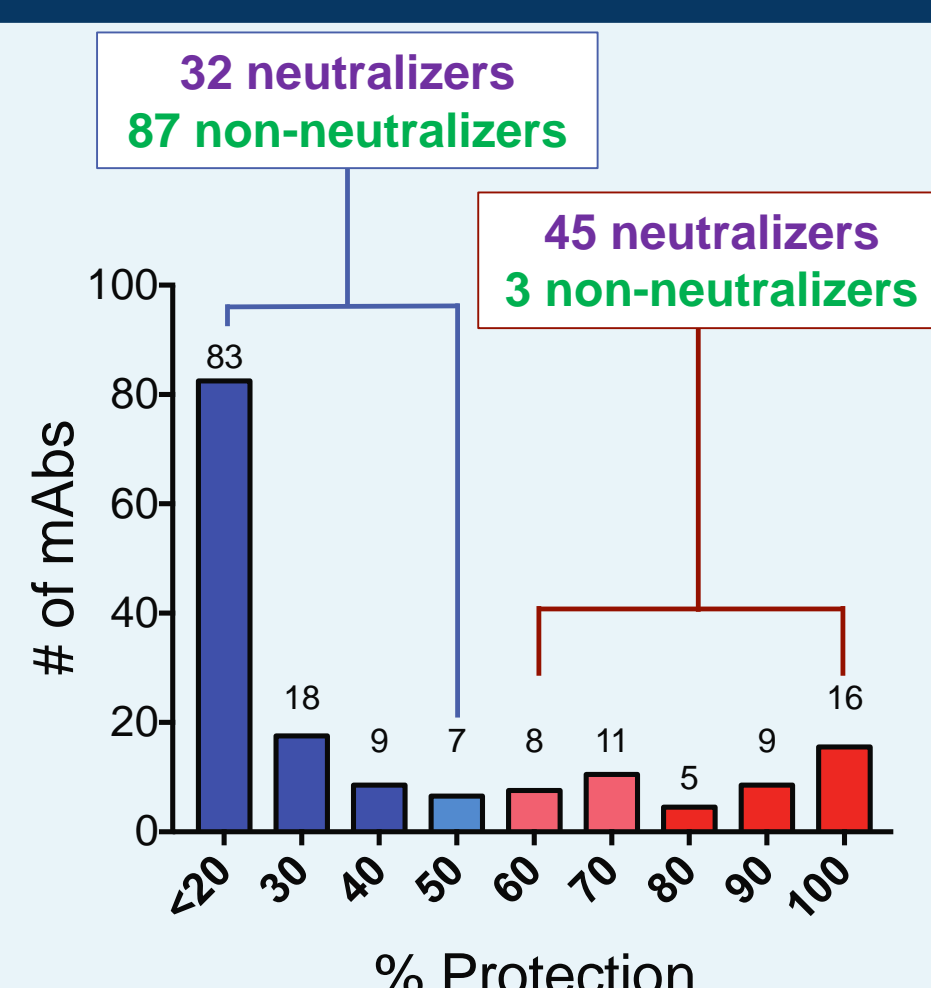
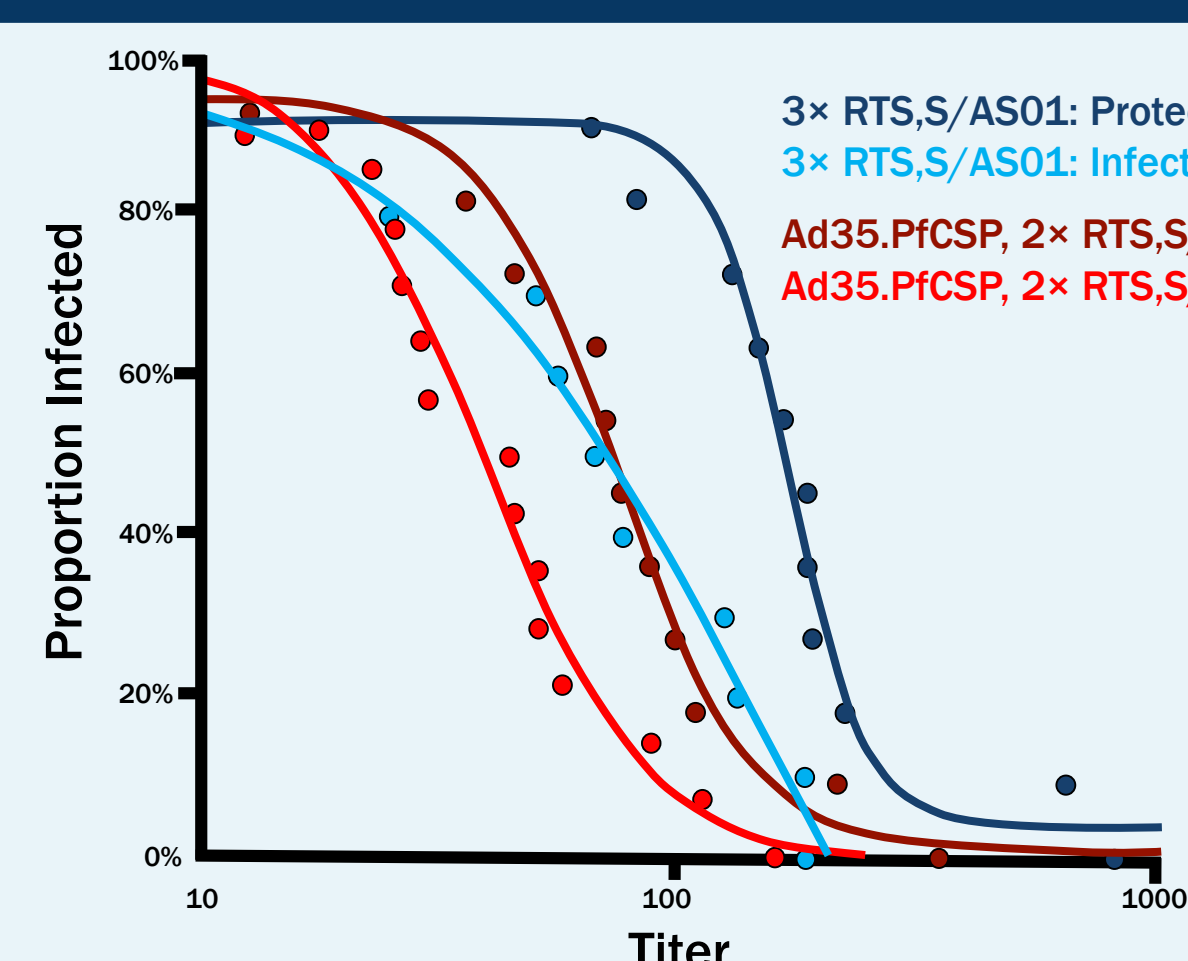


Systems Serology provides new insights for the discovery and development of vaccines and immunotherapies

Todd J. Suscovich and Piers Whitehead

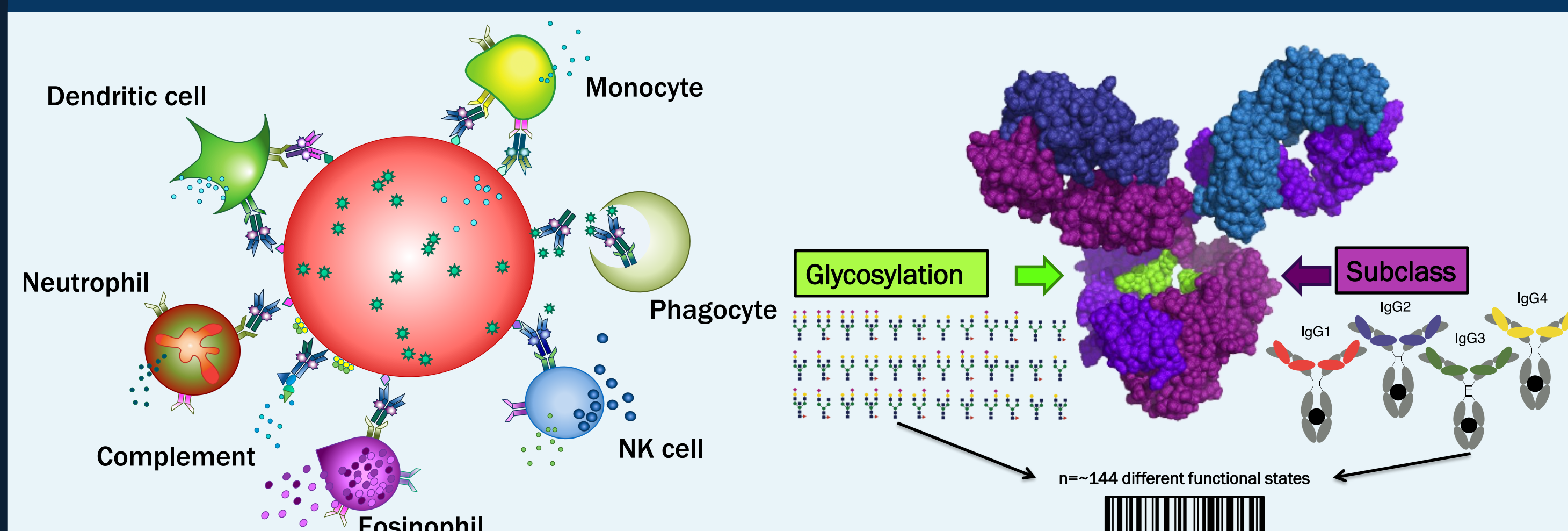


Commonly used antibody features are often poor predictors of protection and efficacy



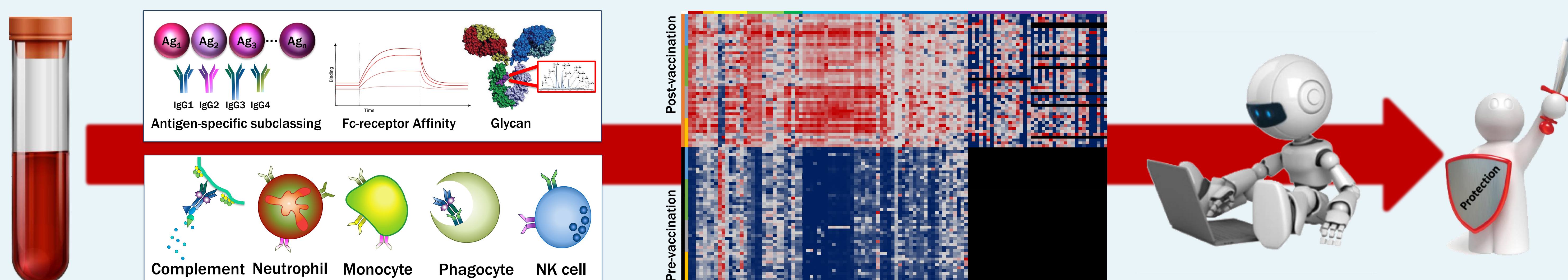
- For many clinically approved vaccines, titer and neutralization activity alone do not mechanistically drive protection, and protection is observable in the absence of neutralization.
- Titer alone provides little insight into the quality of the antibody response; however, evidence accumulated across a spectrum of vaccines has suggested a critical role for numerous antibody functions in protection from a number of clinically relevant pathogens.
- **To better predict protection and efficacy, a deeper understanding of antibody function is required.**

Beyond neutralization, antibodies mediate an array of effector functions



- Antibodies function as molecular beacons, marking pathogens, infected cells, and tumor cells as aberrant and directing the functional activity of the innate immune system to eliminate these threats.
- Antibody functional activity is controlled via two modifications to the Fc domain: antibody isotype/subclass and antibody glycosylation.
- These changes modulate the affinity of antibodies for Fc receptors found on all innate immune cells, functioning as an immunological "bar code" that provides instructions to the innate immune system as to how best to eliminate threats

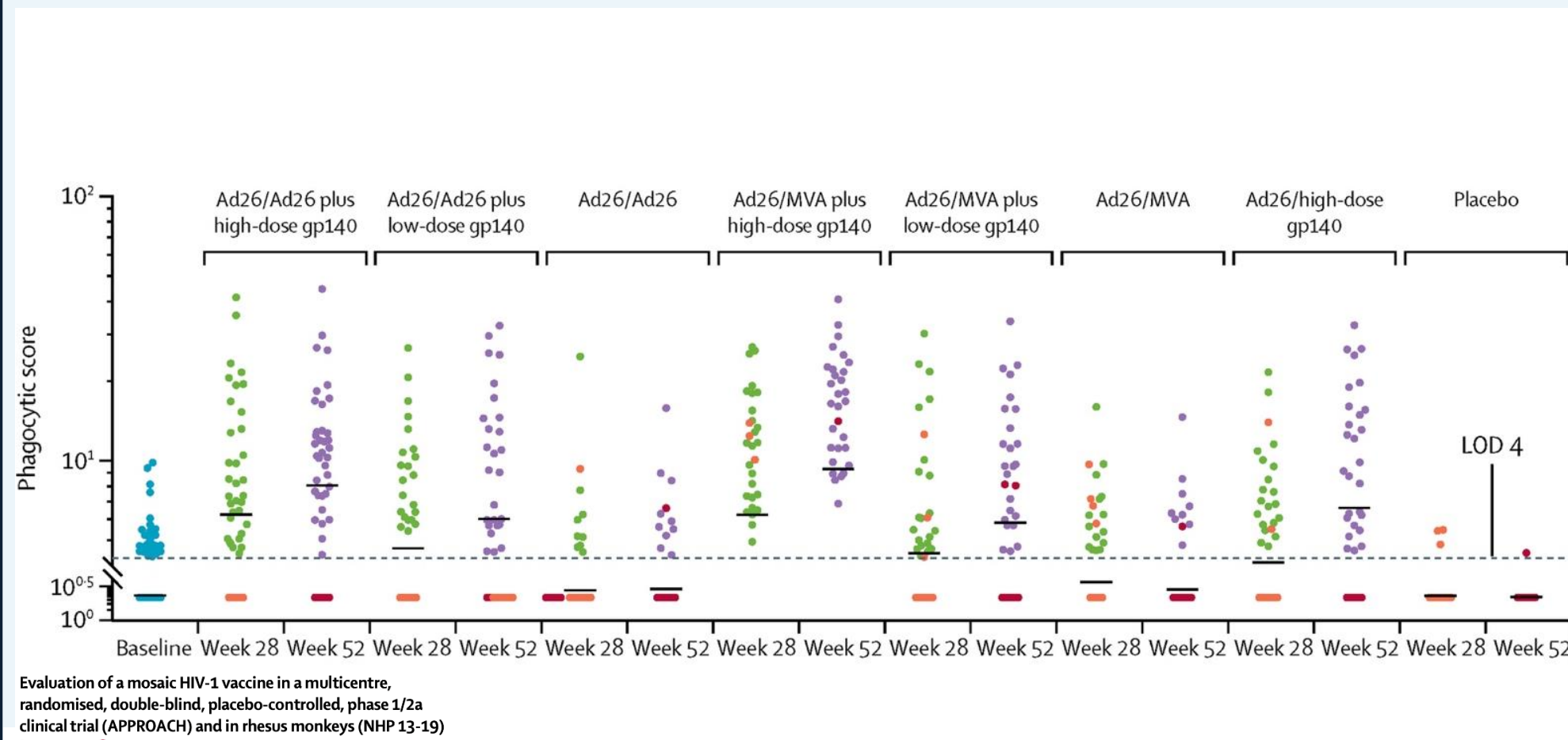
Systems Serology: a high throughput suite of assays that interrogates antibody features and function



- Suite of functional and biophysical assays developed at the Ragon Institute that enables the collection of population-level functional and biophysical antibody profiles.
- Robust, high-throughput, rapid, and highly reproducible bead- and plate-based assays linked to system biology/machine learning algorithms.

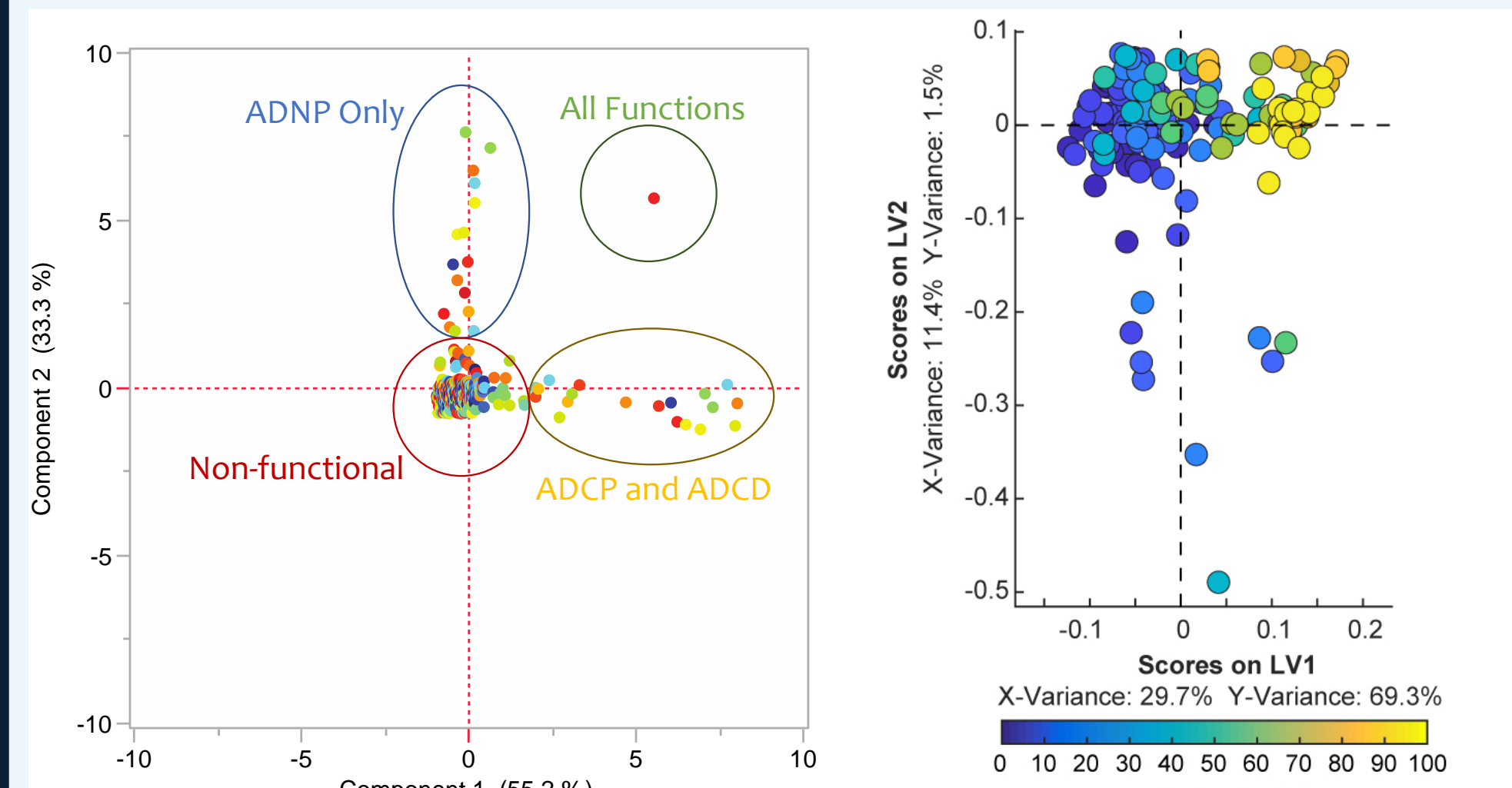
- Easily adaptable to analyze antibody responses against any antigen, both known and unknown.
- Defines the specific characteristics of the most protective humoral immune responses in both monoclonal antibodies and polyclonal pools of antibodies.

Using Systems Serology to guide vaccine design



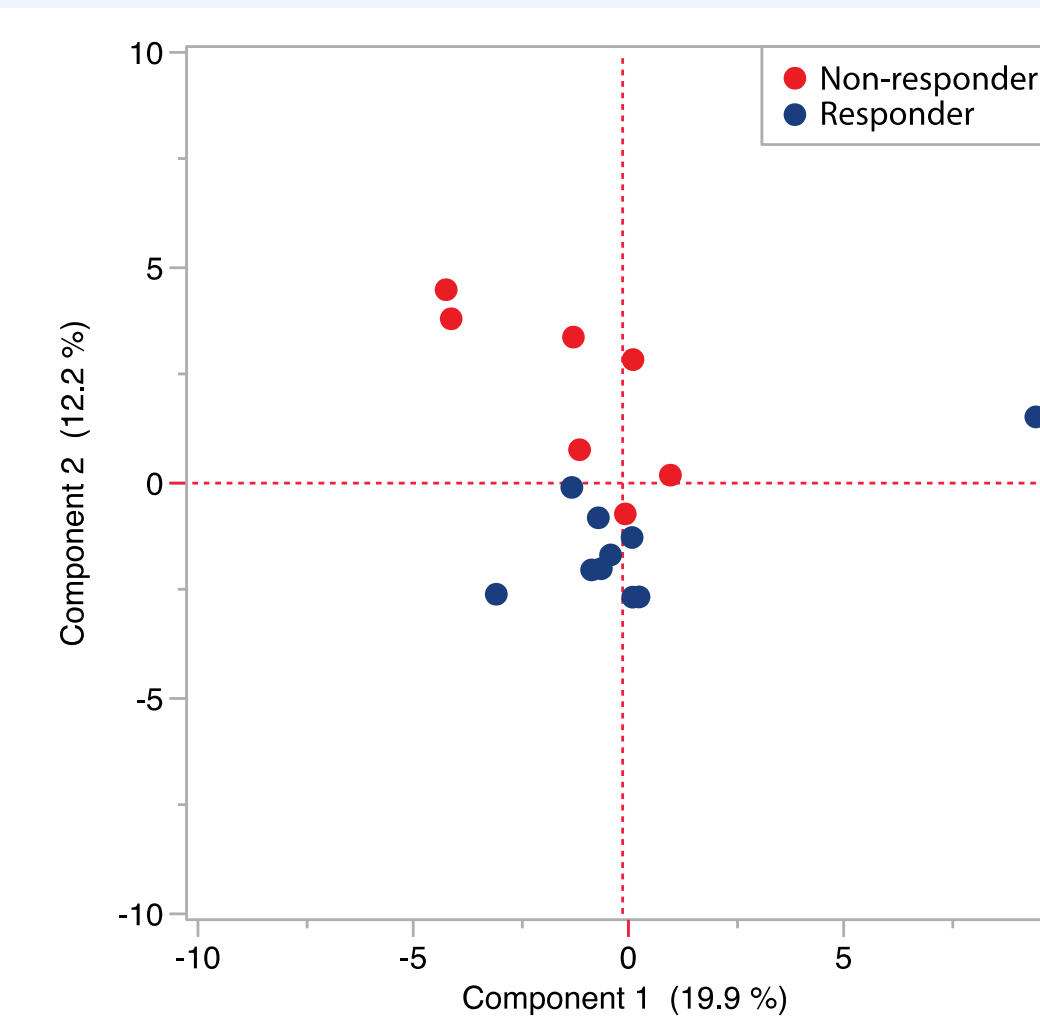
- ❖ Coupled with protection data from pre-clinical studies in animal/human challenge models and early stage efficacy trials, Systems Serology can be used to rapidly profile the full spectrum of antibody functionality and identify correlates of protection.
- ❖ Systems Serology was used to profile antibody functionality in the Phase 1/2a APPROACH study, which evaluated HIV-1 vaccine candidates in parallel human and rhesus monkey studies to define the optimal vaccine regimen to advance into clinical efficacy trials.
- **The identification of antibody features and functions that are linked to protection following vaccination can be used to downselect next-generation vaccines and immunogens to advance further into clinical development.**

Using Systems Serology to make better monoclonal therapeutics



- ❖ Recruitment of innate immune effector functions can be important for the efficacy of monoclonal antibodies in vivo; however, antibodies targeting the same protein can have significantly different functional activities even with the same Fc domain.
- ❖ Systems Serology was used to profile a panel of monoclonal antibodies to identify the antibody functions associated with protection from infection in vivo.
- **The identification of the features can be used to generate highly effective monoclonal antibodies that maximize both ends of the antibody via Fc-engineering to recruit specific functions.**

Beyond infectious disease: Using Systems Serology to predict responders to checkpoint inhibitors



- ❖ Antibodies have an under-appreciated role in clearance of tumors, and neo-antigen-specific B cells and antibodies have been linked to tumor eradication.
- ❖ Systems Serology was used to profile serum taken from melanoma patients before initiation of treatment with checkpoint inhibitors to identify antibody features that could predict successful treatment.
- **The identification of these features will allow for the identification of patients who will respond to specific therapies.**

Conclusions

- Systems Serology can be used to identify potential immunologic and mechanistic correlates of efficacy following vaccination, treatment, or in disease, both within a study and across studies.
- The correlates identified using Systems Serology can be used to guide rational design of vaccines and cancer immunotherapies as well as the development of more effective monoclonal therapeutics.

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