Cryo-EM structures of inhibitory antibodies complexed with Arginase1 provide insight into mechanism of action.

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Human Arginase 1 (hArg1) is a metalloenzyme that catalyzes the hydrolysis of L-arginine to L-ornithine and urea and modulates T-cell-mediated immune response. Arginase-targeted therapies have been pursued across several disease areas including immunology, oncology, nervous system dysfunction, and cardiovascular dysfunction and diseases. Currently, all published hArg1 inhibitors are small molecules usually less than 350 Da in size. Utilizing cryo-electron microscopy we have obtained structures of potent and inhibitory anti-hArg antibodies bound to hArg1. These distinct macromolecular complexes are made up of multiple hArg and mAb molecules and are greater than 650 kDa in size. With local resolutions of 3.5 Å or better we unambiguously mapped epitopes and paratopes for all five antibodies and determined that the antibodies act through both orthosteric and allosteric mechanisms. These hArg1:antibody complexes for the first time present an alternative mechanism to inhibit hArg1 activity and highlight the ability to utilize antibodies as probes in the discovery and development of peptide and small molecule inhibitors for enzymes in general.

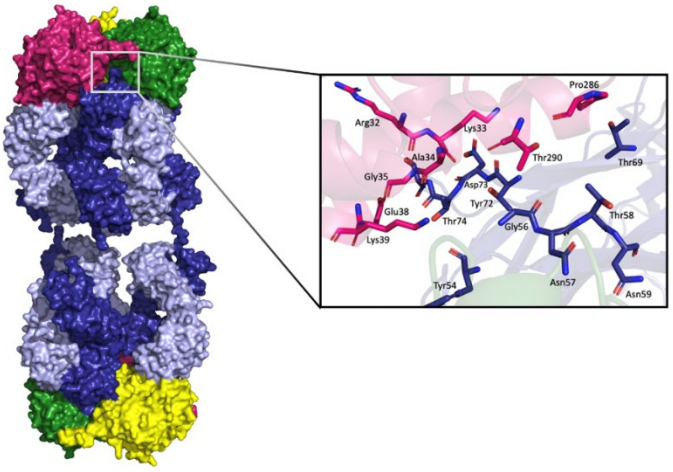

Figure 1