

## **ROBOTIC MECHANISM-BASED QM/MM MATURATION OF A SCAVENGER ANTIBODY MUTATIONALLY BOOSTS ITS PERFORMANCE**

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In vitro selection of antibodies from large repertoires of Ig combining sites using combinatorial libraries is a powerful tool. However, addition of a maturation function is necessary to enable such selected antibodies to mimic more closely the full mammalian immune response. We approached this goal using QM/MM calculations to achieve maturation in silico. We pre-selected an Ig template from a naïve library for its ability to disarm a toxic pesticide related to organophosphorus nerve agents. Virtual screening of 167,538 robotically-generated mutants identified an optimum single point mutation, which experimentally boosted WT Ig scavenger performance by 170-fold. We validated the QM/MM predictions via kinetic analysis and crystal structures of apo-mutant and covalently-modified-Ig, thereby identifying the displacement of one water by an arginine as delivering this catalysis.