We've shown the integral role of the eDNA-DNABII protein lattice in provision of structural integrity to biofilms formed by a broad spectrum of bacterial pathogens and have begun to dissect the mechanism by which these matrix components are released into the extracellular milieu. Exposure of all biofilms tested to date, including those formed by each of the ESKAPE pathogens, to antibodies directed against a DNABII protein induces catastrophic collapse of the biofilm with release of resident bacteria. These newly released bacteria demonstrated a unique phenotype of increased sensitivity to killing by antibiotics that were otherwise ineffective against a biofilm, yet was also significantly greater than that demonstrated by their planktonic counterparts. This collapse of the biofilm, as mediated by DNABII protein-directed antibody, does not require direct contact with the biofilm, is rapid, specific and highly effective both in vitro and in vivo. To better harness the potential power of the DNABII protein-targeted approach, we epitope-mapped these proteins to identify specific protective antigenic domains and used this information to both design a chimeric vaccine candidate as well as to optimize the development of a therapeutic strategy. Both approaches have now been extensively tested in vitro, as well as in three distinct animal models wherein marked biofilm disruption or notably augmented disease resolution were demonstrated, respectively. Disease resolution was also obtained following direct delivery of Fab fragments of antibodies directed against specific domains of a DNABII protein, which thereby indicated that the Fc portion of the antibody was not necessary for effectiveness and suggested a simple model of competitive inhibition. Further, these antisera were synergistic when used in combination with either DNase or traditional antibiotics, as well as when tested for their ability to disrupt multispecies biofilms present within diverse human clinical samples. In a vaccine approach, local or systemic immunization with the chimeric antigen induced the production of antibodies that mediated rapid biofilm disruption and either marked reduction of bacterial load or complete bacterial clearance. Given that the natural adaptive immune response is directed toward non-protective domains of the DNABII proteins, redirection of that immune response by immunization with an antigen designed to mimic protective domains exclusively proved to be a high effective strategy while simultaneously avoiding the potential to drive a pre-existing non-protective response that would have likely been stimulated by immunization with the native protein. We are extremely encouraged by our extensive pre-clinical data and believe we have developed several very promising lead therapeutic and vaccine candidates for further evaluation.