Protein structure determination by X-ray crystallography remains a foundational aspect of structural biology, in spite of the inconvenient fact that the proteins must be crystalline. Given the persistently low protein crystallization success rates of < 20% even in the most sophisticated laboratories, improvements in crystallization outcomes (e.g., crystal formation, quantity, crystallization onset time, diffraction quality, etc.) are needed to help maximize the productivity and structural information produced by macromolecular crystallography facilities. Crystallization can be facilitated by interactions with surfaces, whether intentional or adventitious, and DeNovX’s approach is to use physical or chemical surface modifications to systematically change the energetics of the interactions between the nucleation sites on a surface and the solution to be crystallized. In studies using known crystallizers such as lysozyme, \(-\)lactoglobulin, thaumatin, and bovine pancreatic trypsin, surface energy modifications have reproducibly demonstrated reductions in crystallization onset times of up to 32% vs. controls, and these studies often give more crystals that frequently form in contact with the engineered nucleation sites. As a challenge to the breadth of the approach, improvements in crystallization outcomes have been reproducibly demonstrated for different solutes (proteins and small molecule active pharmaceutical ingredients), aqueous conditions, organic solvents, surface energy motifs, crystallization techniques, and form factors (e.g., microscope slides, vials, capillaries, HTS screening plates, etc.). Systematically tuning the surface energy of the substrate or vessel in contact with the solution to be crystallized has been shown to be an effective way to improve crystallization outcomes while requiring minimal changes to the existing crystallization chemistry and workflow.