The structuring of water near non-polar molecular fragments or surfaces mediates cohesive interactions (so-called hydrophobic interactions) that underlie a broad range of interfacial, colloidal and biophysical phenomena. Substantial progress has been made during the past decade towards understanding hydrophobic interactions in simple model systems, but in most biological and technological contexts, non-polar domains are found in close proximity to polar and charged functional groups. Theories and simulations hint that the effects of nanometer-scale chemical heterogeneity on hydrophobic interactions may be important, but these ideas have not been tested experimentally. In this presentation, I will show that ions immobilized adjacent to non-polar domains can substantially increase or decrease the strength of hydrophobic interactions, with the effect strongly dependent on the specific ion type. By using chemical force microscopy and surfaces presenting alkyl and amine/ammonium (Am) units, we have found that protonation of amines can double the strength of hydrophobic interactions. In contrast, guanidine/guanidinium (Gdm) groups, when co-immobilized with alkyl groups, are found to eliminate measurable hydrophobic interactions. These divergent effects of proximally immobilized cations were confirmed by single-molecule force measurements with sequence-specific oligopeptides. Overall, our results demonstrate that the “hydrophobicity” of non-polar domains is not a property of the species that constitute the domain but rather is strongly modulated by functional groups located as far away as 1 nm. This understanding provides a fresh starting point for optimizing molecular recognition processes as well as the self-assembly of synthetic amphiphiles, colloids, or macromolecules by judiciously placing charged groups near non-polar domains to tune hydrophobic driving forces.