HSP70 isoforms are overexpressed in nearly all types of cancer, but the specific pattern of overexpressed isoforms is yet to be understood. To solve this problem, we have developed a series of high-throughput assays for use in the identification of isoform selective HSP70 inhibitors. These assays have revealed a compound with significant specificity toward the endoplasmic reticular HSP70 isoform, GRP78. This compound has been validated in a series of biochemical, biophysical, and cellular assays we have developed or adapted from the literature. We have also worked to optimize the binding specificity, potency, and *in vitro* pharmacokinetic properties of this compound through medicinal chemistry efforts. Additionally, we have characterized the substrate specificity pattern of the human HSP70 isoforms using machine learning and peptide microarrays. We are using this pattern to predict sensitivity of cancers to specific HSP70 inhibition and to examine the importance of each HSP70 isoform in the process of oncogenic transformation. This project has significant implications in the fundamental understanding of HSP70 function as well as personalized medicine. *Critically, these are not expected to have the same liabilities as HSP90 inhibitors*, as one of the problems leading to clinical challenges with the HSP90s is due to upregulation of the HSP70s, therefore, our approach is addressing a unique aspect of protein quality control.