Stress or heat shock proteins (HSPs) are the most conserved proteins present in both prokaryotes and eukaryotes. Their expression is induced in response to a wide variety of physiological and environmental insults. These proteins play an essential role as molecular chaperones by assisting the correct folding of nascent and stress-accumulated misfolded proteins, and preventing their aggregation. HSPs have a dual function depending on their intracellular or extracellular location. Intracellular HSPs have a protective function. They allow the cells to survive lethal conditions. Various mechanisms have been proposed to account for the cytoprotective functions of HSPs. Several HSPs have also been demonstrated to directly interact with various components of the tightly regulated programmed cell death machinery, upstream and downstream of the mitochondrial events. On the other hand, extracellular located or membrane-bound HSPs mediate immunological functions. They can elicit an immune response modulated either by the adaptive or innate immune system. This review will focus on HSP27, HSP70, and HSP90. We will discuss the dual role of these HSPs, protective vs. immunogenic properties, making a special emphasis in their utility as targets in cancer therapy.