Although heat-shock (cell stress) proteins are commonly considered as being intracellular molecular chaperones that undertake a number of cytoprotective and cellular housekeeping functions, there is now a wealth of evidence to indicate that these proteins can be released by cells via active processes. Many molecular chaperones are secreted, or exist as cell surface proteins which can act as powerful signalling agonists and also as receptors for selected ligands. Levels of heat-shock (cell stress) proteins in biological fluids are now being associated with a plethora of clinical conditions, and these proteins therefore have potential utility as biomarkers of disease and/or response to therapeutic intervention. The present article summarizes current knowledge relating to extracellular cell stress proteins as biomarkers of human disease.