Binding immunoglobulin protein (BiP) or glucose regulated protein 78 (grp78) is a vital, ubiquitous resident of the endoplasmic reticulum (ER). As an intracellular chaperone BiP correctly folds nascent polypeptides within the ER and also regulates the unfolded protein response ensuring protection of the cell from denatured protein reinforcing its anti-apoptotic role when the cell is under stress. Additionally, BiP is a member of the heat shock protein 70 family and, as a stress protein, is upregulated in conditions of reduced oxygen and glucose. Cell stress induces surface expression and secretion of BiP. Consequently BiP is detectable in several bodily fluids including serum, synovial fluid and oviductal fluid. However, as an extracellular protein, BiP has additional properties that are quite distinct from the intracellular functions. Extracellular BiP is immunoregulatory and anti-inflammatory causing: development of tolerogenic DC; induction of regulatory T cells; abrogation of osteoclast development and function; induction of anti-inflammatory cytokine production, including IL-10, IL-1 receptor antagonist and soluble TNF receptor type II; attenuation of TNFα and IL-6. Together these functions help drive the resolution of inflammation. Disease models of inflammatory arthritis have helped to demonstrate the novel mode of action of BiP in which the pharmacokinetics and pharmacodynamics are dissociated. The three murine models to be discussed each show BiP induced long-term therapeutic protection and therefore BiP has the potential to provide long-lasting drug–free therapy in rheumatoid arthritis.