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Nicotinamide adenine dinucleotide (NAD+) biosynthesis from nicotinamide is used by mammalian cells to replenish their NAD+ stores and to avoid unwanted nicotinamide accumulation. Pharmacological inhibition of nicotinamide phosphoribosyltransferase (NAMPT), the key enzyme in this biosynthetic pathway, almost invariably leads to intracellular NAD+ depletion and, when protracted, to ATP shortage and cell demise. Cancer cells and activated immune cells express high levels of NAMPT and are highly susceptible to NAMPT inhibitors, as shown by the activity of these agents in models of malignant and inflammatory disorders. As the spectrum of conditions which could benefit from pharmacological NAMPT inhibition becomes broader, the mechanisms accounting for their activity are also eventually becoming apparent, including the induction of autophagy and the impairment of Ca2+- and NF-κB-dependent signaling. Here, we discuss the rationales for exploiting NAMPT inhibitors in cancer and inflammatory diseases and provide an overview of the preclinical and clinical studies in which these agents have been evaluated.