The transcription factor signal transducer and activator of transcription 3 (STAT3), is a highly sought-after target for the development of cancer therapies and importantly an actionable mediator of resistance to chemotherapy, pathway-targeted therapeutics and radiotherapy. Although a well corroborated target, the clinical application of STAT3 inhibitors remains elusive. We have discovered a series of novel piperidone analogues of curcumin which are potent and selective pSTAT3 inhibitors both in vitro and in vivo. We aim to further develop those compounds preclinically, as stand-alone therapeutics and as combination partners with standard of care and clinically investigated chemotherapy and radiotherapy, aiming to improve the efficacy of avalaible therapies. We will also use a lead compound, VS-43, as a probe to resensitise cancer cells which have become resistant, and for which chemotherapy no longer works, addressing in this way a pressing medical problem. The exact mechanisms of how these combinations work at molecular level will be investigated. We will also exploit a unique, differentiating property of VS-43, that of killing cells in a non-canonical way (non-apoptotic cell death), which is particularly important for cancers which are hard-to-treat because of the mechanisms they have developed to evade apoptosis. Finally, we will look at how individual cells respond to the targeting of STAT3 and identify how these responses relate to sensitivity or resistance to chemotherapy and assess the efficacy of available STAT3 inhibitors. These studies will provide invaluable information for developing this novel class of agents and bringing them closer to the clinic. Additionally, these agents could also make current therapies work better, in more cancer types, or in cancers which no longer respond.