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Sommario/riassunto	Every minute, 34 new patients are diagnosed with cancer globally. Although over the past 50 years treatments have improved and survival rates have increased dramatically for several types of cancers, many remain incurable. Several aggressive types of blood and solid cancers form when mutations occur in a critical cellular signaling pathway, the JAK-STAT pathway; (Janus Kinase-Signal Transducer and Activator of Transcription). Currently, there are no clinically available drugs that target the oncogenic STAT3/5 proteins in particular or their Gain of Function hyperactive mutant products. Here, we summarize targeting approaches on STAT3/5, as the field moves towards clinical applications as well as we illuminate on upstream or downstream JAK-STAT pathway interference with kinase inhibitors, heat shock protein blockers or changing nuclear import/export processes. We cover the design paradigms and medicinal chemistry approaches to illuminate progress and challenges in understanding the pleiotropic role of STAT3 and STAT5 in oncogenesis, the microenvironment, the immune system in particular, all culminating in a complex interplay towards cancer progression.