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Sen and colleagues conducted an exploratory, first-in-human phase 0 trial that showed that intratumoral injection of a STAT3 decoy oligonucleotide during tumor resection surgery could safely reduce STAT3 target gene expression in head and neck squamous cell carcinomas (HNSCC). Modification of the STAT3 decoy by linkage or circularization of the 2 strands increased its stability in vitro, which facilitated systemic administration of the STAT3 decoy in vivo. Intravenous injection of a cyclic STAT3 decoy, but not the parental decoy, decreased STAT3 target gene expression in HNSCC xenografts and significantly suppressed tumor growth. For details, please see the article by Sen and colleagues on page 694.