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Abstract: Nonviral transfections of six low passage human colon cancer cell lines using the artificial beta-catenin/TCF-dependent promoter CTP4 demonstrated a high promoter activity which was 1000- to 70000-fold higher than in HeLa control cells. Luciferase gene expression levels obtained with CTP4 in epithelial-like tumor cell cultures were only slightly lower than with the strong viral CMV promoter/enhancer, whereas in less differentiated tumor cultures CTP4 expression levels exceeded the CMV expression levels up to 28-fold. Three cell lines representing different morphology typical of the original tumors, more differentiated epithelial-like (COGA-5), piled-up (COGA-12), and poorly differentiated rounded-up (COGA-3), were selected for further investigation. Gene transfer was optimized using lipopolyplex formulation of cationic lipid DOSPER and polycaiton PEI25br. Lipopolyplexes enabled up to 1300-fold or 400-fold higher luciferase expression compared to the corresponding lipoplexes or polyplexes, respectively. Lipopolyfection of an interleukin-2 (IL-2) gene expression construct driven by the CTP4 promoter resulted in very high levels of up to 95 ng of secreted IL-2 per 105 cells and 24 h. The lipopolyplexes were also able to transfec multicellular spheroids that mimic the three-dimensional structure of real tumors.