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Inhibition of signaling via erbB-receptors by antibodies that target the Lewis Y-antigen

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Introduction

IGN311 is a humanized monoclonal IgG1 antibody that binds to the Lewis Y (LeY) carbohydrate overexpressed on epithelial cancers. IGN311 potently mediates human effector functions (ADCC, CDC). The overexpression of fucosyltransferases in tumor cells also results in glycosylation of cell surface receptors by LeY. The anti-LeY antibodies IGN311 and its murine parent version ABL 364 therefore might influence the signaling in tumor cells via inhibition of growth factor receptor functions.

Methods

The present study was designed to provide a proof of concept *in vitro*: Two human tumor cell lines, A431 and SKBR3 (vulval carcinoma and breast cancer, respectively) were propagated under standard cell culture conditions, rendered quiescent by serum starvation and stimulated by EGF or heregulin. Cellular effector regulation, growth factor receptor expression and LeY expression were examined.

Results

Both ABL 364 and IGN311 blocked the stimulation of MAP kinase by EGF and heregulin in SKBR3 and A431 cells. The effect was comparable in magnitude with that of trastuzumab and was apparently non-competitive with respect to EGF. Finally, IGN311 and ABL 364 inhibited EGF-stimulated [3H]thymidine incorporation in A431 cells.

Conclusions

Taken together, the observations show that antibodies against carbohydrate determinants of erbB-familiy members are capable of blocking signaling. The clinical profiling of the humanized monoclonal anti Lewis Y antibody IGN311 has been initiated. Presently a Phase I dose-escalation trial in cancer patients is ongoing.