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BIOTEC PHARMACEUTICALS

EPIDERMAL GROWTH FACTOR: ANTI-TUMORAL TOO?

HAVANA, CUBA—The discovery a few years ago—that the *v-erbB* oncogene encodes a truncated form of the human epidermal growth factor receptor (EGF-r)—provided a first look at the structural biochemistry underlying malignant cell transformation. And the subsequent findings—that a number of human neoplasias (including squamous cell carcinoma and breast cancer) are characterized by elevated levels of EGF-r—have made therapeutic approaches targeted to the receptor very attractive. Most of the protocols presently being developed rely on monoclonal antibodies directed against the receptor, or recombinant fusions of the ligand (EGF) and a cytotoxin. Until now no one had seriously considered that saturating these over-expressed receptors with EGF alone might have clinical utility.

Yet that is exactly what Ramón Fonseca and Rolando Pérez of the Cuban National Center for Oncology and Radiology reported in a recent seminar at the country's Center for Genetic Engineering and Biotechnology. The rationale behind this unique approach, as explained to the scientists who produce the recombinant EGF used in the trials, was provided by a series of consistent papers, from various laboratories and dating back to 1981, showing that high-concentrations of EGF can inhibit the *in vitro* growth of a number of human cancer cell lines.

After laboratory demonstrations that subcutaneous administration of EGF to mice also inhibited incorporation of ^3H -thymidine into the DNA of Ehrlich ascites tumor cells *in vivo* (Lombardero, Pérez and Lage, *Neoplasma* 33:423, 1986), the team designed an animal-model protocol using athymic mice. And when they were able to produce a transient inhibition of tumor growth in both vulvae epidermoid carcinoma (A431 cell line) and lung epidermoid carcinoma (CPH3) xenografts by recombinant human EGF at 20 mg/kg, they were encouraged to begin human trials.

For the pilot trial, the investigators chose ten advanced skin carcinoma patients who had unsuccessfully responded to conventional therapies.

The photomicrograph on the left, from a biopsy of tumor tissue before treatment (25x), shows an abundance of tumor cells with very few stromal cells. The picture on the right was taken three weeks after local administration of EGF and shows a completely opposite situation—very few tumor cells and a strong stromal reaction.

IMAGE
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The photograph shows a patient with a squamous cell skin carcinoma before (left) and after (right) three weeks of daily treatment with a topical creme containing one microgram per gram of recombinant human epidermal growth factor.

None of the patients received any treatment for at least four weeks before the study. Skin carcinomas were chosen for two main reasons: the patients could be constantly followed in the clinic with direct observation of their tumors, and the nature of the lesions allowed a topical administration of the EGF, ensuring a pharmacological concentration *in situ*. In fact, immunohistochemical evidence of EGF penetration into tumor tissue was obtained with anti-EGF monoclonal antibodies.

After daily topical administration of a one percent silver sulphadiazine creme containing 10 µg/gm of recombinant human EGF for three weeks, the researchers obtained two partial remissions, and five patients showed an intense evaluable objective clinical response as measured by a dramatic change in the macroscopic morphology of the lesions. Even those patients

who did not demonstrate an objective clinical response nonetheless showed no progression of their malignancies.

The microscopic anatomy of the EGF-treated tumors was perhaps even more dramatic. Six of nine evaluated patients showed degeneration of tumor cells, marked enhancement of stromal tissue, and an acute inflammatory reaction.

While continuing to treat and evaluate these first patients, the research team is beginning a larger study, and collecting biochemical data on the number and occupancy of the receptor sites, both on the tumor cells and the newly resident stromal cells. In light of these results, the constantly expanding relationships between growth factors, their receptors and the oncogenic process, may now have to be further expanded to include the direct therapeutic use of the hormones themselves. —Harvey Bialy