INTRODUCTION

The idea of attacking cancer cells at the cell surface was revived in the past decade by the availability of monospecific heteroantisera. Phase I trials using monoclonal antibodies to most tumor cell antigens have shown little anti-tumor activity (Reviewed in 1,2). The reasons for these failures are complex, but include heterogeneity of tumor antigen expression; antibody-induced antigen modulation from the cell surface; formation of human anti-mouse antibodies; and the uncertain efficacy of the host cell anti-tumor response (1,2). Immunoconjugates employing monoclonal antibodies as carriers for toxins, drugs, or radioisotopes and chimeric human-mouse monoclonal antibodies remain under investigation (1,2).

We have taken a slightly different approach to this problem by using cell surface growth and nutrient receptors as targets for monospecific antisera. For the past 5 years, these reagents have been developed under the auspices of a National Cooperative Drug Discovery Group with Dr. John Mendelsohn as the Project Leader and Hideo Masui at Memorial/Sloan Kettering Cancer Institute, Dr. Ian Trowbridge at the Salk Institute and myself, with the assistance of National Cancer Institute staff.

A variety of evidence suggests that many tumor cells require growth factors for proliferation, and that growth factor receptor display alters tumor cell behavior (3-5). Our goal has been to develop anti-cancer agents which inhibit tumor cell growth by both marshalling immune responses, and by directly depriving cells of
epidermal growth factor (EGF) receptor stimulation or transferrin receptor function. In contrast to serotherapy targeting other cell surface antigens, in this setting, antibodies inducing antigen modulation may reduce available tumor cell growth factor receptors, and may be as effective as reagents which block or inhibit growth factor receptor action. These reagents have also been useful for studying tumor cell growth factor responses and antigen expression (6-12).

ANTIBODIES TO THE EPIDERMAL GROWTH FACTOR RECEPTOR

Background

The EGF receptor is the prototype ligand-stimulated, protein tyrosine kinase receptor and is highly homologous to the erb-b1 oncogene (13). In vitro studies indicate that the EGF receptor is over-expressed in many different tumor types, and suggest these receptors contribute to the transformed cell phenotype. In vitro, a variety of non-hematologic tumor cell lines express EGF receptors, including lung, bladder, breast, colon and vulvar squamous cell carcinomas (14-22). Many of these same tumors contain RNA for and express the polypeptide growth factor transforming growth factor-α (TGF-α), which binds to and stimulates EGF receptors, and induces a transformed cell phenotype in vitro (23). Recent studies showed that a membrane bound form of tumor cell TGF-α also mediates EGF receptor stimulation (24,25), and indicate that TGF-α can cause transformation without being secreted into the extracellular environment. This potential auto-secretory loop between TGF-α producing tumor cells and endogenous, overexpressed EGF receptors provides a strong rationale for attacking the EGF receptor with monoclonal antibodies (MAbs).

Expression of normal EGF receptors at high density in normal murine fibroblasts by transfecting these cells with a human EGF receptor gene construct causes EGF-dependent cell transformation (13,26), indicating that the native receptor can induce abnormal cellular behavior. When sublines of a squamous cell carcinoma xenograft were implanted in immune-deficient mice, tumor growth rate was positively related to surface EGF receptor number (27).