I will attempt to make two points in this review: (a) "Real" (i.e., operating) cancer surgeons who do research should do applied research, or at least focus their research on "interface areas" not generally within the sphere of interest or even the awareness of the basic scientist. (b) The successful integration of an active clinical cancer surgeon’s practice and research interests (basic or clinical) can be targeted to improving his or her patients’ outcome; this is one (but certainly not the only) straightforward answer to the question "What is a surgical oncologist?" (1).

Each of the experimental lines that our group is now pursuing started after thorough discussion (including both clinicians and scientists) of specific clinical dilemmas.

Clinical dilemma no. 1: Why do poorly differentiated gastrointestinal (GI) tumors behave badly?

Derived scientific tactic: Can the biologic properties/markers that define aggressiveness of poorly differentiated, signet ring, or highly mucinous subsets of GI cancers be applied to better predict which of the more heterogeneous, less predictable, moderately well-differentiated (MWD) (the "wild" type of gastrointestinal cancer) cancers will be a bad actor?

This question has led to two experimental lines.

1. A. Mercurio et al., L. B. Chen et al. (fellows: G. Daneker, O. Wiltz, E. Lee, L. Breen) have studied epithelial tumor/basement membrane interactions (2), matrigel model elucidation (3–5), poorly differentiated colorectal cancer/increased laminin binding (6–8), colon-specific integrin family member receptors α6/β4 (9,10), and cadherin/actinin–α6/β4 interaction in tumor cell adhesion and invasion (11).

2. P. Matsudaira et al., L. B. Chen et al., P. Thomas et al., J. Summerhayes et al., and H. Sears et al. (fellows: R. Bleday, T. Dodson, R. Salem, R. Staniunas, K. Mafune, J. D’Emilia, T. Weber) have focused on the definition of phenotypic/genotypic markers for non-carcinoembryonic antigen (CEA)-producing GI cancers (12–16), elucidation by subtractive hybridization of libraries to define genotypic “uniqueness” in poorly differentiated or metastatic colorectal cancer (17–21), and application of developmental/differentiation-related molecules as markers to map the normal adult large bowel and to define specific changes occurring during transformation in either single or multiple stem cells throughout the gastrointestinal crypt (22–27).

Clinical dilemma no. 2: Why are particular subsets of patients with CEA-producing colon or rectum carcinomas predisposed to liver- or lung-predominant metastatic or recurrent disease? This question, of course, is derived from the clinical findings that, by and large, only those patients with liver or lung failure after primary colon or rectum carcinoma treatment show concurrent or preceding serial plasma CEA increases of any significance.
Derived scientific tactic: What is the function of CEA in the normal and in the transformed enterocyte? This question derives from the realization (rather long in coming) among some clinicians that CEA probably was not evolved to allow surgeons to perform second-look exploration!

This dilemma has led to several experimental lines.

1. N. Zamcheck et al. and P. Thomas et al. (fellows: H. Wagner, S. Meterissian, T. Petrick) have sought to describe the enterohepatic circulation of CEA and CEA-related molecules (27-29) and to verify and isolate specific Kupffer cell or alveolar macrophage-binding moieties on the CEA molecule (30-35). They have also studied the modulation of tumor CEA production by transfection or antisense modulation with subsequent structure/function correlates (work in progress; 36-39).

2. K. Jessup et al. and P. Thomas et al. (fellows: S. Meterissian, H. Wagner, T. Petrick, S. Ishii) have developed xenotransplantation models to help define target-specific metastasis mechanisms (39,40) and investigated CEA function in homophilic or heterophilic adhesion pathways (work in progress; 41-43; Ishii et al., unpublished material).

3. I. Summerhayes et al. (fellows: S. Pories, T. Weber, H. Wagner, J. D'Emilia, A. Joyce) have developed embryonic and "normal" tissue models that allow constitutive expression after transfection with specific known or candidate oncogenes or proto-oncogenes with subsequent structure/function assessment (45-51).

This outline represents how we choose to study what we study in the lab. What about the other direction (i.e., the translation of science to the patient)? Our group's basic design maxim is to focus on areas where we perceive the most acute clinical need and where we already have in hand all necessary clinical and basic research expertise and resources (including patients and disease-related tissues, sera, etc.). I will attempt to illustrate in some detail, using two examples of current "marker" application, chosen because they may represent the first significant clinical fruits born from our long dedication to translational research. The initial clinical application of sucrase isomaltase (SI) and of mitochondrial dyes in colorectal carcinoma (CRC) have occurred at opposite ends of the natural history spectrum of colon and rectum carcinomas.

The clinical application of SI represents an incremental biochemical and subsequent immunohistochemical deployment of what had earlier been described by others as a possible developmental antigen present throughout the embryonic gut but retained only on the cell surface and/or in the cytoplasm of adult human small bowel. Our laboratory showed that this molecule was expressed in transformed large bowel and, most important, in dysplastic lesions (including known precancerous GI conditions, such as ulcerative colitis, gastric dysplasia, and Barrett's esophagus, and large villotubular polyps with morphologically defined dysplasia). Experimental design during the clinical application of SI has been influenced by the clinician's understanding of the limits in reproducibility, in sampling bias, and in qualitative (not quantitative) morphologic definitions of progressive dysplasia. At present, the state-of-the-art predictors for "transformation about to happen" throughout the gastrointestinal epithelium are inadequate, and the outcome for patients with inflammatory bowel disease or Barrett's esophagus is critical. Our goal in the application of SI as a phenotypic and, eventually, genotypic marker is to provide a reproducible, quantitative predictor of which patients at risk of GI transformation might benefit by surgical preemption (i.e., proctocolectomy, subtotal resection, esophagogastrectomy, etc.).

Collaborators in the application of genotypic and phenotypic markers to fresh or archival human specimens over the years have included H. Sears, B. Wolf, H. Goldman, C. O'Hara, B. Andrews, R. Mayer, K. Jessup, and many of our clinical gastroenterology and cancer surgery colleagues. Specific application of SI has been possible only because of our unique interaction with Harvey Goldman and other pathologists in his department. Without Dr. Goldman's expertise in the morphologic descriptors of inflammatory bowel disease, gastric dysplasia, and other known GI premalignant states, the need for more quantitative (possibly field change related) molecular markers of transformation could not have been addressed (52-54).

SI had been looked at by others a number of years ago as a potential developmental antigen in normal adult gut differentiation but was not found to have any differential expression between normal adult colon and colon or rectum adenocarcinoma.