*Original Article*

# Immunohistochemical Identification of Tumor Markers in Metastatic Adenocarcinoma

## *A Diagnostic Adjunct in the Determination of Primary Site*

RICHARD W. BROWN, MD,[1] LAURJ BROZO CAMPAGNA, MD,' J. KAY DUNN, PhD,[2] AND PHILIP T. CAGLE, MD1

Adenocarcinoma that metastasizes from an unknown primary site is a significant oncologic problem. With the exception of prostate-specific antigen and thyroglobulin, no single immunehistochemical marker is entirely site specific. A retrospective study was undertaken to determine whether a panel of markers could accurately predict the site of origin of common metastatic adenocarcinomas. On the basis of reports of their relatively restricted specificity for carcinomas of colon, breast, lung, ovary, and upper gastrointestinal tract (stomach, pancreas, and bile duct), eight markers were selected for simultaneous evaluation: gross cystic disease fluid protein-15, breast cancer antigen 225 (BCA225), 1372.3, DF3 (CA15-3), carcinoembryonic antigen (CEA), CA19-9, CAl25, and estrogen receptor. The study population consisted of 128 metastatic nonmucinous adenocarcinomas for which the primary site was known. Staining was performed on formalin-fixed, paraffin-embedded tissue usi an enhanced-sensitivity avidin-biotin peroxidase comple

The most informative markers were CEA, CA19-9, CAl25, and BCA225. With this four-marker panel, the most predictive multiple-marker phenotypes, as determined by a combination of area under the receiver operating characteristic curve, specificity, and percent correct predictions, were CEA+, BCA225–, and CAl25- for colon tumors; BCA225+, CEA–, and CAl25– for breast tumors; BCA225+, CEA+, and CA19-9– for lung tumors; CAl25+ and CEA– for ovarian tumors; and CEA+, CA19-9+, and CAl25+ for upper gastrointestinal tract tumors. Overall, these phenotypes correctly predicted the known primary site in 66% of cases. Until single highly sensitive and specific markers are developed for adenocarcinomas other than prostate and thyroid tumors, the origin of a metastatic adenocarcinoma can best be suggested or excluded with clinicopathologic data combined with a panel of selected immunohistochemical markers. (Key words: Adenocarcinoma; Immunohistochemistry; Metastases; Tumor markers) Am J Clin Pathol 1997;107:

Metastatic adenocarcinoma of unknown primary site is a significant oncologic problem, constituting 600/0 of all such metastatic cancers.[1] Unequivocal identification of the primary site is essential for breast, ovarian, and prostate carcinomas because specific effective treatment regimens are available for these tumors.[2] In many additional cases, the treating oncologist who knows the site of origin may elect additional treatment options, such as resection of solitary metastases from colorectal carcinoma or immunotherapy for renal cell carcinoma. Although extensive radiographic and endoscopic examination may be performed in an effort to discover the primary site, this approach is time consuming, expensive, and inconvenient; has the potential to cause morbidity; and in the majority of cases is unsuccessful.[2] A more directed search or unequivocal identification of the primary site by the pathologist would clearly be advantageous.

In a number of previous immunohistochemical studies, single tumor markers including prostate-specific antigen (PSA),[M] thyroglobulin,[5] B72.3 (TAG-72),[6,7] breast cancer antigen 225 (BCA-225),[8-11] gross cystic disease fluid protein-15 (GCDFP-15),[12,13] carcinoembryonic antigen (CEA),[14,15] CA19 CAl25,[19-20] CA15-3 (DF3),[1821] and placental alkaline phosphatase[22] have been applied to primary adenocarcinomas from various sites in an attempt to demonstrate site-specific patterns of immunoreactivity. With the exception of PSA and thyroglobulin, which are highly specific for prostate and thyroid carcinomas, respectively,[3-5] no single commercially available marker has proved entirely site specific. Until single markers are available that are site-specific for other common adenocarcinomas, an alternative approach is to use a

*From the Departments of [?]Pathology and [2]Medicine, Baylor College of Medicine and The Methodist Hospital, Houston, Texas.*

Supported by an award from the Moran Foundation, Houston, Texas.

Manuscript received February 14, 1996; revision accepted August 14, 1996.

Address reprint requests to Dr Brown: Department of Pathology, The Methodist Hospital, 6565 Fannin, MS 205, Houston, TX 77030.