Monoclonal Antibodies for Imaging and Therapy of Prostate Cancer

Neil H. Bander

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INTRODUCTION

It has been known for the better part of a century that antibody–antigen interactions are characterized by great sensitivity and specificity. As a result of these attributes, a substantial proportion of in vitro diagnostic testing relies on antibody-based assays to detect disease-related antigens. In 1975, with the development of hybridoma technology by Kohler and Milstein (1), the application of antibody-based technology took a giant leap forward. This technology resulted in the production of monoclonal antibodies (MAbs) and allowed, for the first time, production of unlimited quantities of identical antibody molecules, each to a defined antigen. The significance of this technology was recognized by the bestowing of the Nobel Prize on Kohler and Milstein in 1984. Virtually all immunoassays are now routinely performed with MAbs rather than conventional polyclonal antiserum. However, development of this technology for use in vivo, as might have been anticipated, has taken quite a bit longer.

At this point in time, several MAbs have been approved by the Food and Drug Administration (FDA) for in vivo imaging of neoplastic and nonneoplastic diseases. Furthermore, therapeutic use of antibodies has also been FDA-approved in several disease settings, including transplantation, coronary artery disease, inflammatory bowel disease, arthritis, and most recently, cancer. In the past 1–2 yr, antibodies have now been FDA-approved for the treatment of non-Hodgkin’s lymphoma and breast cancer. A large number of antibodies continue in various phases of clinical testing in other cancer settings. This chapter will review the application of MAbs for in vivo diagnostic and therapeutic use in prostate cancer (Pca).

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MAB FOR IN VIVO IMAGING OF PCA

Background

It is generally agreed that the clinical staging of Pca, be it the local, regional, or systemic extent of disease, leaves room for significant improvement. The traditional workup to define the regional and systemic extent of disease has consisted of a bone scan and computed tomography (CT) or magnetic resonance imaging (MRI). Although bone scans clearly have increased sensitivity over the metastatic bone survey, they still lack sensitivity and specificity. Attempts to evaluate the pelvic lymph nodes with CT or MRI have proven particularly ineffective. These imaging modalities define metastatic nodes strictly by size, i.e., nodes >1 cm are defined as abnormal. By definition, therefore, nodal involvement <1 cm is interpreted as normal and, conversely, inflammatory or hyperplastic nodes >1 cm might be erroneously read as neoplastic. As a result, CT and MRI lack both sensitivity and specificity. One study (2), which primarily examined the ability of sonography and MRI to evaluate the local extent of disease, also provided data on the ability of MRI to detect nodal disease. In this study, 185 patients had both MRI and pelvic lymph node dissection. Twenty-three of the 185 (12%) patients were found at surgical pathology to have nodal involvement; the MRI was able to detect only 1 of the 23 (4%). Similarly, low sensitivity has been noted in CT studies (3). Because of these poor results, CT and MRI have been all but abandoned for pelvic lymph node staging.

Current Status of MAb Imaging

Systemically administered MAbs, by being able to circulate and bind to a specific, tumor-related antigenic target, offer promise to increase both the sensitivity and specificity of current imaging techniques. In the case of Pca, a prostate organ-specific antibody would suffice. Any accumulation of such a prostate organ-specific antibody outside of the prostate itself would indicate metastatic Pca.

Initial attempts to image Pca began with MAbs to the established prostate-related antigens, prostate-specific antigen (PSA), and prostatic acid phosphatase (PAP) (4–6). In retrospect, although these antigenic targets were adequately specific, they were compromised by significant shortcomings, thereby explaining their failure. Neither PSA nor PAP is expressed at the cell surface, but rather they are secreted antigens. Lack of cell-surface expression precludes cell-associated antibody binding. Furthermore, presence of antigen in serum, often at substantially elevated levels, effectively served to “decoy” the MAbs away from the tumor site, thereby both lowering any true “signal” as well as increasing “background.”

Subsequently, another murine MAb, originally designated 7E11-C5.3 and later renamed CYT-356, was developed. This MAb (7) recognizes prostate-specific membrane antigen (PSMA). PSMA has been studied in several laboratories, and has now been cloned, sequenced (8), and characterized. PSMA has optimal characteristics for antibody targeting:

1. It is highly prostate-restricted (9–17).
2. It is expressed at high levels by most prostate cancers (9,10,12,13,15,16).
3. Expression increases as tumor grade increases (12,15,16).
4. Expression increases in metastatic sites (12,15,16).
5. Expression further increases as the tumor becomes androgen-independent and hormone-refractory (12,15).