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Opinion Article

Micro Tumor Molecular Imaging with Berep4: Toward Theranostics for Basal Cell Carcinoma

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Introduction

The most prevalent cancer in humans, Basal Cell Carcinoma (BCC), appears macroscopically and microscopically identical to many other skin lesions, making differential diagnosis challenging. With the goal of improving the precision and accuracy of diagnosis, we are developing a method for quantitative molecular imaging of BerEP4, a tran's membrane biomarker for BCC. The purpose of this pilot study was to determine the affinity and selectivity of BerEp4 antibody and to see if it could be used to develop theranostic probes for BCC. We show that a film/pellet phantom can be used to recover individual signal increases using our photon-counting fluorescence macro detection method. Furthermore, we demonstrate that a two-photon stimulated fluorescence/backscatter confocal imaging system can view the BerEP4 antibody/antigen combination on the surface of BerEP4-expressing cancer cells in three dimensions.

BerEP4 appears to be a viable biomarker for molecular imaging of BCC based on preliminary findings. We investigated the feasibility of imaging BCC with varied histologist using a combination macro/micro-optical method to prepare BerEP4 for eventual theranostic usage. These optical approaches, which allow for real-time monitoring of treatment, may pave the way for non-invasive diagnosis, treatment, and follow-up.

The most prevalent cancer in humans is Basal Cell Carcinoma (BCC). Over the last few decades, the annual incidence has risen rapidly, reaching 2.8 million new cases in the United States alone. When the annual incidence of no melanoma skin cancer was just 0.5 million in 2004, the direct costs of diagnosis and treatment were reported to be $1.4 billion in the United States. Early detection and treatment of BCC and other skin malignancies has become an increasingly critical public health concern due to a tendency toward younger ages at initial diagnosis.

Skin cancer is less common than benign solitary skin lesions such as actinic keratosis (a premalignant skin lesion) and seborrhea keratosis (a benign skin lesion). Actinic keratosis and seborrhea keratosis, especially in the early stages, might have clinically comparable appearance to BCC. It's difficult to tell the difference between benign and malignant tumors, especially since the clinical practice of detecting skin cancer hasn't altered much in the last 100 years. BCC and other skin cancers are detected with a skin biopsy, which is followed by a histologic examination of the specimen and surgical treatment, which comes with a high price tag and a high risk of complications.

Micro Tumor Molecular Imaging

Dermoscopy, which is used to aid early identification of skin cancer, is one of the currently available clinical methods that improve clinical diagnosis above simple visual inspection. However, due to their subjective character and the limitations of visual assessment, their utility is limited. In a recent retrospective assessment of 2,000 specimens submitted to the Pinkus Dermatopathology Laboratories (Monroe, MI) by a mixed group of academicians and private practitioners to rule out BCC, we discovered that more than 70% were benign lesions.

At varied depths and tumor cell collection sizes, BCC can present with a range of histologic morphologies. Variants that are micro nodular, infiltrative or morpheaform penetrate deeper. They also have a significantly smaller number of cancer cells, necessitating a modality that can image sufficiently deep while maintaining good signal detection sensitivity. Because of secondary events such as inflammation, the visual perception of BCC and other skin malignancies can be deceiving. As a result, a large field of view is required to reduce sampling error. "Macro-optics" is a crucial component of a hybrid multimodal system since it allows for deeper imaging with a broader field of vision.

Because of the microscopic profile of skin structures and cutaneous diseases, the majority of primary skin optical imaging research has been done at the microscopic level. One of the limiting factors in imaging the entire lesion has been the narrow field of view. As a result, there is a bottleneck in a dermatological clinic's workflow. Furthermore, due to the microscopic nature of skin disorders and their histopathology similarities, a focused and quantified procedure is required to achieve the necessary diagnostic accuracy and precision. In the diffuse regimen, we used time-resolved fluorescence imaging as the preferred method.

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Our ultimate goal is to have a product that can be used at the bedside. To objectively monitor treatment, molecular signals must be quantified using time-resolved macro fluorescent imaging. Localized subcellular resolution with three-dimensional tomographic image reconstruction may also be accomplished when the microsystem is combined with a Two-Photon Excited Fluorescence (TPEF)/confocal multimodal imaging system. NIR is the ideal spectrum for this application due to the compatibility of Near-Infrared (NIR) lasers with both macro- and micro-optical systems.

In vivo optical imaging with an NIR fluorophore–labeled antibody is a well-established approach. BerEP4-expressing carcinomas have been imaged using NIR fluorophores coupled with BerEP4 Ab. BerEP4 or EpCAM, a 40-kDa type 1 Trans membrane glycoprotein with an extracellular domain found on chromosome 4q, is a human epithelial cell adhesion molecule. The basolateral surface of simple, pseudo stratified, and transitional epithelium expresses this biomarker. It's in vivo expression is linked to epithelial proliferation and dedifferentiation, according to the researchers. BerEP4 has been found to be overexpressed in a variety of carcinomas, including all histologic variations of BCC and colorectal carcinoma, making it a promising pan carcinoma biomarker with diagnostic and therapeutic (theranostic) potential.

BerEP4 is found in 90% to 95% of BCC cancers. BerEP4 is also seen in various eccrine and apocrine glands, as well as follicular lesions such trichofolliculoma. However, these lesions make only a small percentage of the biopsies taken to rule out BCC. Most importantly, BerEP4 is not expressed in normal skin's stratified epithelium or benign lesions that are frequently biopsied to rule out BCC due to clinical morphologic similarities in the early stages. As a result, BerEP4 is a promising biomarker for BCC molecular imaging.