JOINT TRANSNATIONAL CALL 2016:

"Minimally and non-invasive methods for early detection and/or progression of cancer"

PARTNER REQUEST/COLLABORATION OFFER

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☑ YES

SEARCH FOR A COLLABORATOR

IF YOU ARE LOOKING FOR A PARTNER IN YOUR SUGGESTED PROPOSAL, PLEASE SPECIFY ALSO THE NEEDED EXPERTISE

Project proposal
Project title (draft): Clinical diagnosis of cancer using fibrous mat-based capture assay of circulating tumor cells
Short description of the project in preparation and of the consortium; description of the areas of expertise needed (Max. 2000 words): Conventional in vitro circulating tumor cell (CTC) detection methods are always limited by the blood sample volume because of the extremely low abundance of CTCs among the large number of hematologic cells. The aim of this study was to overcome this limitation by designing and constructing an in vitro CTC capture assay. We blended poly(sulfobetaine methacrylate) (PSBMA) and poly(acrylic acid) (PAA) into nylon-6 through electrospinning to generate a fibrous mat-based capture assay of CTCs. The contents of nylon-6, PSBMA, and PAA in the electrospun triple-blend fibrous mats (ETBFMs) were optimized to avoid degradation and to balance between the non-biofouling behavior and the antibody immobilizing efficiency. In addition, we examined the capture ability of CTCs for clinical diagnoses of colorectal cancer, in comparison with the results identified through pathological analyses of biopsies from colonoscopies. For nine individuals with stage II, III, and IV colorectal cancer, our CTC detection with ETBFMs provided complete positive expression. Two of four individuals were diagnosed to possess stage I colorectal cancer. Two of seven individuals without colorectal tumor, as identified through pathological analyses of biopsies, exhibited positive expression of CTCs. These positive results suggest that such ETBFMs are promising materials for in vitro CTC capture assays. Thus, in this population, the static fibrous mats exhibited sufficiently considerable capture efficiency for the diagnosis of colorectal cancer from unknown specimens. Pathological analyses of biopsies from colonoscopies generally require a doctor, a nurse, and an anesthetist, and at least one week for positive identification. CTC detection using static fibrous mats significantly decreases the required manpower and time, providing great potential for rapid cancer screening. (Journal of Materials Chemistry B, 2016, 4, 6565-6580) In this work, anti-EpCAM was exploited to modify the surface of the fibrous mat. However, the anti-EpCAM is not only specific for colorectal cancer but also other cancers, such as breast and prostate cancer, resulting slight false positive in the real clinical diagnoses. We have the resources to fabricate the materials and proceed clinical experiments with IRB. Therefore, we are looking for a partner who could provide the anti-body or other compound with higher specific interaction with each kind of cancer.

OFFER FOR COLLABORATION

IF YOU PROPOSE YOURSELF AS A PARTNER IN A CONSORTIUM, PLEASE DETAIL YOUR EXPERTISE

Short description of the areas of interest and expertise (Max. 2000 words):

Metastasis is the most common cause of cancer-related death in patients with solid tumors. A considerable body of evidence indicates that tumor cells are shed from primary and metastatic tumor masses at different stages of malignant progression. These breakaway circulating tumor cells (CTCs)1 enter the bloodstream and travel to different tissues of the body as a crucial means of spreading cancer. The current gold standard for diagnosing the tumor status requires invasive biopsy and pathological analysis. In addition to conventional approaches, detecting and characterizing CTCs in patient blood provides an opportunity for early diagnosis of cancer metastasis. To address this unmet need, significant research endeavors, especially in the fields of chemistry, materials science, and bioengineering, have been devoted to the development of CTC detection, isolation, and characterization technologies. Identifying CTCs in blood samples has, however, been technically challenging, due to the extremely low abundance (a few to hundreds per milliliter) of CTCs among a large number (10^9 mL^{-1}) of hematologic cells.

Recent studies have demonstrated the prognostic importance of CTC detection in patients with lung cancer, breast cancer, colorectal cancer, melanoma, and prostate cancer. Given its great value in the clinical management of cancer patients, the detection of CTCs has become one of the hottest research topics. In recent years, several technologies have been established for sensitive and specific detection of CTCs through different working mechanisms, such as immunomagnetic separation using capture agent-coated magnetic beads, microfluidics-based technologies that enhance the frequency of cell–substrate contacts, and microfilter devices that isolate CTCs based on differences in size. Taking full advantage of the unique interactions between cellular surface components and nanostructured materials, a vertically oriented silicon nanopillar array, coated with epithelial cell adhesion molecule antibody (anti-EpCAM14), has exhibited outstanding cell capture efficiency (40–70%) when employed to isolate viable cancer cells from peripheral blood samples. In contrast to the other CTC enrichment approaches, nanostructured material-based CTC enrichment and detection uniquely mimics the nanoscale interactions observed in biological systems.

Inspired by the nanoscale features embedded in cellular surface components (e.g., microvilli, filopodia) and extracellular matrix (ECM) scaffolds, significant research endeavors have been devoted to the study of the interactions between live cells and nanostructuredmaterials (e.g., nanofibers, nanotubes, nanopillars) that share similar dimensions with cellular surface components and ECM scaffolds. Researchers have gained an understanding that nanostructured materials can affect cellular behavior—for example, their adhesion, viability, migration, differentiation, and morphology. For the development of cell-capture assays, much research effort has been dedicated to exploring the unique interactions between nanostructured materials and cells. Electrospinning is a simple and versatile nanofabrication technique for the preparation of ultralong nanofibers with controllable diameters (from a few nanometers to several micrometers). A diversity of soluble and fusible polymers can be electrospun to form respective nanofibers from their precursor solutions. Electrospun nanofibers have potential for use in a wide range of applications—for example, as biocompatible/biodegradable scaffold matrices in tissue engineering. Although nylon is widely used as a biomaterial because of its outstanding physicochemical properties, it is a relatively inert polymer. Novel and convenient methods would be necessary if we are to modify nylon surfaces to obtain better non-biofouling and the immobilization of antibodies for CTCs. Zwitterionic poly(sulfobetaine methacrylate) (PSBMA) is a novel superhydrophilic polymer that has been widely

explored in biomedical applications as an ultralow-biofouling material that resists the adsorption of proteins, cells, and bacteria. Antibodies cannot be covalently linked to PSBMA using 1-ethyl-3-[3-(dimethylamino) propyl]carbodiimide (EDC) and N-hydroxysuccinimide (NHS) chemistry, because its lacks carboxyl or amino groups. In this study, we developed a simple method employing poly(acrylic acid) (PAA), a rich carboxylic polymer, as a coupling reagent to immobilize streptavidin and, subsequently, anti-EpCAM antibody. In this approach, we blended three polymers—nylon-6, PSBMA, and PAA—with formic acid to fabricate a highly rough surface through a one-step electrospinning process. After immobilizing anti-EpCAMto the surface, we used the electrospun triple-blend fibrous mats (ETBFMs) of nylon-6/PAA/PSBMA to capture CTCs from 7 mL specimens of blood from unknown subjects in vitro. Considering the geometric orientation of the nanostructures embedded in ECM scaffolds, electrospun nanofibers better mimic these horizontally oriented nanostructures, potentially leading to improved cell–substrate affinity. Therefore, pseudopodium could extend itself until the actin reassembles itself into a network.

In addition, surface grafting on electrospun fibers usually proceeds in themonomer solution for several hours. Compared with surface grafting on electrospun fibers, blend electrospinning could readily reduce the fabrication time consumed. Other advantages of using electrospun nanofibers include (i) precise control over the dimensions and packing densities of the nanofibers; (ii) deposition of the nanofibers onto any given substrate (e.g., silicon, glass) using a well-established experimental setup; and (iii) the feasibility of engineering a variety of organic materials onto a cell capture substrate. The challenges associated with CTC detection and analyses begin with the natural scarcity of CTCs at early stages of malignant progression. The aim of this study was to develop a platform for CTC detection with high sensitivity, specificity, and reliability. Therefore, low attachment of leukocytes and high attachment of CTCs on the surface are two important characteristics to enhance CTC recognition. The strategy of our project is to generate bio-nonfouling properties and appropriate roughness with anti-body grafts on the surface to improve CTC–substrate affinity specifically. We have diagnosed nineteen individuals who participated in a colorectal health check program, including colonoscopy biopsy with pathological analysis and the withdrawal of 7mL of blood samples for CTC detection, and evaluated the efficiency of our CTC capture assay. Note that the blood samples from nineteen individuals were completely unknown before CTC detection. All of these individuals were not patients, but might feel colorectal uncomfortableness leading to their participations in this colorectal health check program. The diagnosis of colorectal cancer could be made by negative or positive expression of CTCs for these individuals after six hours behind the colonoscopy process. One week later, final recognition through pathological analysis revealed the diagnosis results with the stage of colorectal cancer for these individuals. For nine individuals with stage II, III, and IV colorectal cancer, our CTC detection with ETBFMs provided complete positive expression. Two of four individuals were diagnosed to possess stage I colorectal cancer. Two of seven individuals without colorectal tumor, as identified through pathological analyses of biopsies, exhibited positive expression of CTCs. These positive results suggest that such ETBFMs are promising materials for in vitro CTC capture assays. The results suggest that CTC detection using static fibrous mats significantly decreases the required manpower and time, providing great potential for rapid cancer screening.