

REVIEW ARTICLE

## Diagnosis and treatment of the Cancer Tumor Cells (CTCs); Capturing and Diagnosing Kits

Ali Alirezaie Alavijeh<sup>1</sup>, Masoomeh Dadpay<sup>2\*</sup>, Farid Barati<sup>1</sup>, Mohammad Barati<sup>3</sup>

<sup>1</sup> Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord, Iran

<sup>2</sup> Department of Pathology, Medical Faculty, AJA University of Medical Sciences, Tehran, Iran

<sup>3</sup> Department of Applied Chemistry, Faculty of Chemistry, University of Kashan, Kashan, Iran

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### ABSTRACT

**Objective(s):** In the developed countries, one of the leading causes of death is cancer. Cancer cells with their unique and destructive characteristics impose high costs on communities.

**Methods:** In this study, we will review the latest cancer researches and diagnostic tools.

**Results:** Existing technologies, using clinical markers and studying the polymeric screeners of cancer cells, have created kits that make cancer diagnosis at early stages. The study of the survival mechanism in malaria and honey bee and the development of bacterial engineering has created new approaches to create powerful tools for cancer detection and control.

**Conclusions:** The completion of these processes will create the potential for cancer eradication. Study of the survival mechanisms in nature and purposive modeling of it will lead to provide many solutions to solve the problems. These studies can lead to develop accurate diagnostic and therapeutic tools.

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## INTRODUCTION

Cancer is one of the leading causes of death in the developed countries, despite the increasing advances in science. Some of the most important limiting factors in the treatment of this disease include lack of access to the tumor, the risk of critical organs surgery, and cancer spreading to other parts of the body. Nowadays, concurrent treatments are used to manage cancer. When a therapist provides two different methods for treatment of two patients (and no more) in the same time, a concurrent treatment is in progress. The therapist should be in the supervising and performing room all minutes provided to patients [1]. The new studies on cancer and its diagnostic tools are reviewed in this study. Characteristics of Cancer Cells include generating growth signals, inactivation of growth inhibitory signals, cell death resistance, Arteriogenesis, and

invasion. Also, energy management and escaping from the immune system are considered as other characteristics of cancer cells. Cancer cells consume glucose and generate lactic acid and citric acid under anaerobic conditions [2].

The cancerous cells spread throughout the body are able to diagnose and assess the stage of the disease [3, 4]. These cells provide valuable information for treating the patient. The ratio of cancer cells to circulating tumor cells (CTCs) is 1 to 10 [5], therefore separation, maintenance and cultivation are challenging for therapeutic strategies [6, 7]. The migration of 0.01% of cancer cells to other organs produces secondary tumors [7, 8]. These are circulating tumor cells (CTCs) and have  $10^7$ – $10^9$  WBCs per 1 mL of blood [6]. Hence, high precision is needed for their identification and separation.

\* Corresponding Author Email: [mdadpey1@yahoo.com](mailto:mdadpey1@yahoo.com)



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### THE DIFFERENCE BETWEEN NORMAL AND CANCER CELLS

One of the first signs of cancer can be found in the serum of patients and is caused by immune cells. The immune system produces specific, stable and identifiable antibodies for the antigens related to each tumor that lead to detect the disease in its early stages [9-11]. This method can be used to identify colorectal cancer in the early stages. Bowel or colon cancer also is known as colorectal cancer (CRC) and occurs when the development of cancer is from rectum or colon. The annually 700,000 deaths shows that the CRC is a common cancer [12]. Change in the bowel movements, continuous feeling tired, blood in the stool, and weight lost are the symptoms and signs of CRC. This method has been used for breast cancer [13], liver [14], lung [15] and stomach, successfully [16]. The size of cancer cells in the blood is different from others. According to this property, micrographers are developed to isolate and mark the cancer cells (Fig. 1) [5, 17, 18].

### MARKERS USED IN KITS FOR CANCER DIAGNOSIS

The cancer developed from esophagus is esophageal cancer. Weight lost and difficulty in swallowing are two common symptoms of this cancer. However, it can cause hoarse voice, dry cough, enlargement of lymph nodes around

the collarbone, and coughing up or vomiting blood in the patients. This cancer is diagnosed using salivary specimens and miR-10b, miR-144, miR-21 and miR-451 markers [20]. Also, serum, milk and urine specimens can be used to diagnose breast [21], prostate [22], bladder [23] and stomach cancers [15, 24, 25]. The markers used to diagnose these cancers include TGF- $\beta$ , PSA, Exosome size, and autoantibodies, respectively.

### DIAGNOSTIC KITS FOR CANCER

Various companies have begun to develop diagnostic-economic kits based on various markers around the world, which are listed in the following table (table1) [26]. Depending on the type of test used for liquid-based cytology (LBC), the conventional cytology (CC) can be replaced with LBC as primary test method [27]. Considering cost-effectiveness, it is necessary to know whether other LBC systems are more desirable [28]. Seegene and BioSewoom are two famous companies that first one main concentration is on diagnosing infectious disease and the second one predominantly produces molecular diagnostic kits for cell blood cancer. The annual average growth rate of diagnostic kits for cancer in next generation is 42.6% that initiate from \$1.8 billion in 2014 which sharply escalates to \$10.629 billion in 2019 [29].

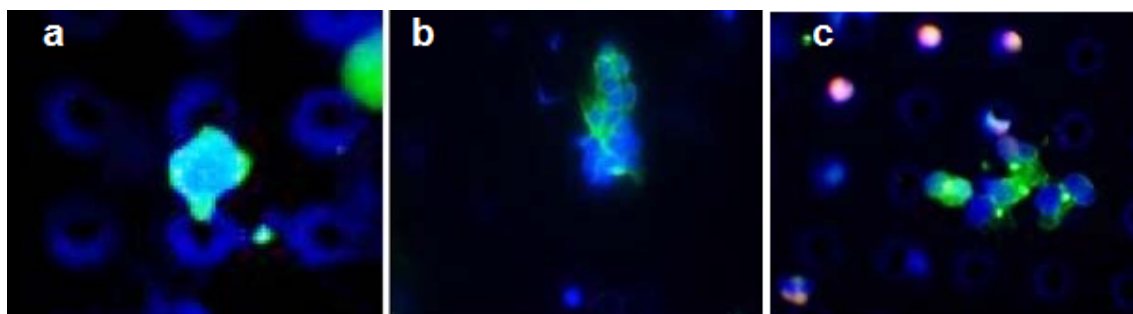


Fig. 1. Different size of cancer cells; (a) Breast cancer, (b) Lung cancer, (c) Prostate cancer [19]

Table 1: Some useful biomarkers for diagnosing cancer in manufacturing kits[26].

Company	Cancer	Cancer marker	Test time	Specimen
Biotech	prostate	PSA <sup>1</sup>	15 minutes	Whole blood, serum or plasma
Vita	cervix	OncoE6	2.5 hours	Swab of cervix
Biotech (IP)	Liver	AFP <sup>2</sup>	10 minutes	Whole blood, serum or plasma
Cortez	Breast - Lung	CEA <sup>3</sup>	10 minutes	Serum or plasma

<sup>1</sup> Prostate-specific antigen (PSA)

<sup>2</sup> Alpha fetoprotein

<sup>3</sup> Carcinoid embryonic antigen

## THE DIAGNOSTIC PERFORMANCE MECHANISM OF KITS

Plastic strips are used to perform cancer diagnostic tests, these strips consist of the following parts: 1. Place of specimen with marker; 2. Antibody –binding pad; 3- Antibody diagnose line; 4- Control identification line (To evaluate the performance of the test). In the diagnostic test process, the specimen is placed along the strip in two test lines to evaluate the result and in the control line for the accuracy of the test performance. In the first step, the antibodies available at this stage will reveal cancer markers if present and the accuracy of the test will be displaced with a line created from the binding of the antibodies available at the beginning of the strip and its markers in the control line location [30].

## USE OF POLYMER IN DIAGNOSIS AND ISOLATION OF CANCER CELLS

Some of the most important applications used in the medical field includes screening, polymer coating and marking in solutions [31-33]. Parylene polymers [5, 34, 35], polyurethane methacrylate [36], filters Poly (dimethylsiloxane) (PDMS) [37] have been used for separation of circulating cancer cells from the body. Microfilters are designed using these polymer structures to trap cancer cells based on their physical characteristics (Fig. 2). Polymers coating is their second approach to cope with cancer, which polymeric binding polymers [38, 39] and PEG [32] are used to achieve this purpose. Therefore, nanoparticles are combined with these polymers for cancer cells marking. The third group

of polymers refers to polymers that prevent the movement of the circulating cancer cells by binding them. For example, alginate polymers, dendrimers [33] and 3-Mercaptopropyltrimethoxysilane can be mentioned in this regard [40].

## MODELING AND USING NATURE TO DIAGNOSE AND TREAT CANCER

### *Malaria and Marking Cancer Cells*

Malaria as an important infectious disease is considered as an important cause of death, annually. It is an infectious disease affecting humans and animals that is borne by a mosquito. This disease is caused by a parasitic single-celled microorganisms belonging to the Plasmodium group [41]. Three of the species of plasmodium falciparum, it is known as the leading cause of death [42, 43]. Malaria is multiplied in the body using liver cells and red blood cells [44-46]. Epithelial surface molecules are used to identify and trap circulating cancer cells due to the different sizes of cancer cells. Marking and screening of the cancer cells with the mesenchymal origin due to its small amount of the molecules is associated with deficiencies [47-49]. Hence, specific proteins are needed to identify cancer cells that these proteins are not found in normal cells.

Chondroitin sulfate (CS) is composed of similar units of disaccharide modified with sulfate groups. This molecule is expressed on the cancer cells surface, the placenta and the epithelial and mesenchymal origin cells. Chondroitin sulfate is able to bind to 30 different proteoglycans, that are expressed on the surface of tumor cells in the primary stages and metastases [50, 51]. The

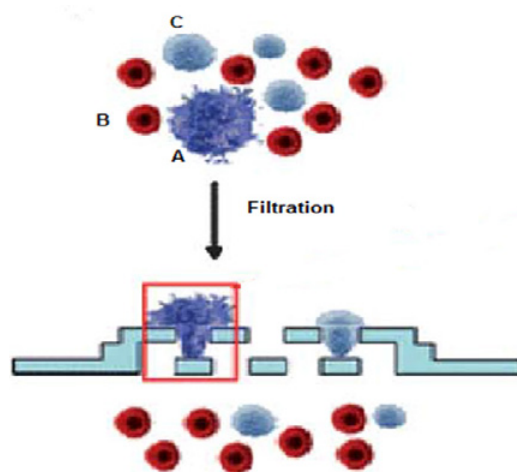


Fig. 2. Screening of Cancer Cells by Polymers; A) Cancer Cells, B) Red Cells, and C) White Blood.

VAR2CSA protein of the malaria parasite has a good ability to identify the Chondroitin sulfate in target cells [26]. Therefore, the recombinant of CS-binding VAR2CSA protein (rVAR2) is able to trap cancer cells of the prostate, lung, liver and pancreas with minimal contamination of other blood cells [52].

#### *Anti-tumor effect of bee venom*

Bee venom has a chemical composition with different compounds such as melittin. Melittin is an antitumor peptide composed of 26 amino acids [53-56]. The antitumor effect of this peptide on prostate, breast, lung and liver cancers has been confirmed in previous studies. This substance causes the death of cancer cells by activating *metalloproteinase-2*, caspase and phospholipase A2 [55, 57-59]. Other reported effects of bee venom on cancer cells include apoptosis, growth suppression [60] and angiogenesis. Chemotherapy complications can be improved with combining this substance with chemotherapy drugs which leads to increase therapeutic effect and reduce doses [56].

#### *Cancer diagnose and bacterial cancer therapy*

As the relationship between bacteria and cancer (H. pylori and pancreatic Cancer) is being studied and the results are published [61], bacteria are used for treatment of a variety of diseases, such as cancer [62-64], by carrying nucleic acid to host [65]. Salmonella typhimurium and Listeria monocytogenes are two bacterial species used in cancer management [66, 67]. Typhimurium bacteria copes with cancer cell disease by disturbing the metabolic process of cancer cells [68, 69] and Listeria monocytogenes bacteria by reducing the growth of cancer cells by removing Interleukins (ILs) factors [66, 67]. Another application of the bacteria is their abilities to act as diagnostic sensors in the body [70], so that, the simultaneous growth of some of these bacteria are used to diagnose cancer [71].

#### **TUMOR-ON-A-CHIP PLATFORMS**

Tumor-on-a-chip devices have been developed to investigate the efficiency of treatments on cancer patients. These devices can be strongly helpful for development of cancer treatment methods [72]. They are able to show the metastatic properties of cancer tumors. Tumor-on-a-chip devices have a great potential in development of drug delivery systems based on nanoparticles (NPs).

The drug delivery based on nanotechnology has advantages such as higher drug specificity, higher water solubility, and higher therapeutic efficiency compare to conventional cancer treatment methods. Furthermore, no drug resistance occurs through treatment duration because of direct delivery of anticancer drug to the tumor [73, 74].

#### **CONCLUSION AND VISION**

Circulating cancer cells have disrupted the cancer treatment process. Therefore, this disease with high mortality can be managed by creating higher-sensitivity identification and treatment processes. Engineering and modeling of natural conditions for diseases initial diagnosis as well as the treatment of them, particularly cancers, can lead to introduce new technologies in the diagnosis and treatment fields. Study of the survival mechanisms in nature and purposive modeling of it will lead to provide many solutions to solve the problems. As mentioned earlier, the study of the survival mechanism in malaria, honeybee and engineering bacteria can introduce different approaches to diagnose cancer. These studies can lead to develop accurate diagnostic and therapeutic tools.

#### **CONFLICT OF INTEREST**

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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