

Short Communication

A Promising Application of Gold Nanoparticles-Capped with Bispecific Antibody Therapy against Breast Cancer

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Keywords

- Breast cancer; Bispecific antibody; Gold nanoparticles; Targeted delivery; Diagnostic tools

Abstract

Nanobiotechnology has prompted new and improved materials for biomedical applications with particular emphasis in gene and drug therapy, imaging and diagnostics. Most recently, drug delivery and targeting of molecular therapeutics for cancer is gaining momentum to overcome existing drawbacks such as toxicity and side-effects. 'Proteomics' and 'genomics' have emerged as challenging areas of nanomedicine. This short communication tries to summarize a portion of most advanced developments in immunotherapy application using noble metals like gold nanoparticles as carriers especially for breast cancer therapy.

ABBREVIATIONS

BC: Breast Cancer; mAb: Monoclonal Antibody; IgG: Immunoglobulin; BsAbs: Bispecific Antibodies; EGFR: Epidermal Growth Factor Receptor; RNA: Ribose Nucleic Acid; DNA: Deoxyribose Nucleic Acid; CTCs: Circulating Tumor Cells; PEGylated: Polyethyleneglycolated; scFv: Single Chain Fv Fragment; SERS: Surface Enhanced Raman Spectroscopy; cfNAs: Cell-Free Nucleic Acids; ctDNA: Cell-Tumor DNA; SNVs : Somatic Single Nucleotide Variants; CAN: Copy Number Alterations; SVs : Structural Variants; PCR: Polymerase Chain Reaction; ICP-MS: Inductively Coupled Plasma Mass Spectrometry

INTRODUCTION

Breast cancer is one of the life threatening diseases of several types of cancer globally causes over 500,000 deaths, annually. Conventionally, anti-cancerous agents are being used to block essential functions of cancer cells and kill dividing cells. Unfortunately, the resulting in harmful side effects such as cardiotoxicity is inevitable that restrict dose and duration of treatments reducing their potential effectiveness. Recent drug development has focused on targeted therapies using nanoscale site specific drug delivery approach that have less toxicity and minimal side effects [1]. Further, antibody-based therapy for cancer has become an established strategy for treating patients with different kinds of tumors with reduced side-effects, significantly [2]. The use of mAbs in treating uncontrolled growth of cancer is not uncommon. Especially, certain surface proteins such as receptor tyrosine kinases are biomarkers and over expressed in many cancers and have become vulnerable targets

[3]. Researchers are focusing on synthesis of bio-conjugates of human antibodies engineered to bind specifically to molecular targets present on the surface of cancer cells. Such engineered antibodies are indistinguishable from the natural antibodies produced in the body in response to antigens of tumor. These specially engineered antibodies basically retain their natural Y-shaped structure and exhibit variable antigen binding region of the molecule that has been designed to bind specific epitopes of BC cell surface molecules. Recently, investigators have joined their hands on the EU-funded ReBAT (Develop a fully human bispecific antibody (Biclonic™) production technology platform and...) project exploiting this technology to produce human antibodies to treat BC. The joint efforts of the Merus Bionics® (Netherlands) and ChromaCon Ltd. (Switzerland) has led to develop cheaper and safer antibody therapeutics of a fully human bispecific IgG1 mAb (now called bsAb) that is capable of binding two targets simultaneously. This new knowledge of bsAb therapeutics was based on their previous generation and preclinical development of a human therapeutic bispecific antibody targeting EGFRs such as HER2 and HER3 in BC.

In the last decade, the biological application of nanoparticles has been extensively used including bio-detection, drug delivery and diagnostic imaging, particularly in the field of BC diagnostics and treatment [4]. In BC diagnostics, fluorescent nanoparticles can be used for multiplex simultaneous profiling of tumour biomarkers and for detection of multiple genes and matrix RNA with fluorescent *in-situ* hybridization [5,6]. Three crucial biomarkers are being constantly used in BC to detect and accurately quantify single tumour sections by use of

nanoparticles conjugated to antibodies. The use of conjugated nanoparticles is obviously promising to allow at least ten cancer-related proteins to be detected on tiny BC tumour sections or blood borne CTCs, providing a new method of analyzing the proteome of an individual tumour. In the near future, super magnetic nanoparticles have exciting possibilities as contrast agents for BC detection *in vivo*, and for monitoring the response to treatment.

In the recent decade, GNPs have emerged as potential candidates for research and application in biomedical sciences owing to their geometrical, optical, and surface chemical properties. They are being used in various fields include genomics, biosensors, immunoassays, clinical chemistry, site targeted drug delivery and imaging. The use of PEGylated-GNPs as diagnostic and therapeutic agents involves selecting the appropriate targeting component such as an antibody or an antibody fragment such as scFv and attaching it on to the surface of GNPs by a skilled worker [7]. The attachment strategy can either be non-covalent or covalent. The non-covalent approaches involve either electrostatic or hydrophobic interactions or strategies where both these interactions are involved. In the non-covalent approach the antibodies are nonspecifically adsorbed onto the surface of GNPs via both electrostatic and hydrophobic interactions [8]. Hydrophobic interactions between the antibody and GNP are due to the interaction between hydrophobic parts of antibody (protein) and the metal. The antibodies comprise positively charged amino acids and also the N-terminal acids which electrostatically interact with the GNPs thereby forming non-covalent bonds. Rayavarapu et al., used the non-covalent approach to bind mouse monoclonal anti-body specific to HER2 to GNPs for application as SERS, and molecular probes for optical imaging techniques to detect the location of the tumor [9,10].

When monoclonal anti-body specific to HER2 capped to GNPs are mixed with suspected BC patient's blood plasma or serum, immediately, a protein corona is formed on the GNPs surface due to the adsorption of antibody specific proteins in the BC patient's blood to the GNPs. Using a two-stage GNP-enabled dynamic light scattering assay, as the BC progresses the amount of anti-body specific to HER2 in the protein corona is increased in comparison to non-cancer controls. The increased amount of anti-body specific to HER2 found in the protein corona is believed to be associated with the auto antibodies produced in response to cancer antigenic proteins as a part of immunodefense [11].

Proteomic analysis of the nanoparticle protein corona revealed molecular profile differences between cancer and non-cancer serum samples in liquid biopsy screening test for CTCs [12]. Auto antibodies and natural antibodies are produced in BC patients in response to tumorigenesis. The test may be applicable for early detection and risk assessment of an advanced stage of BC. This novel blood test is well suited for screening on the spot appears to be simple and low-cost procedure that requires only a few drops of blood sample, and the results are obtained within minutes. Also, the adsorption of antibodies on the GNP surface may be replaced by other molecules in biological samples as the bonding is mere adsorption to distinguish heterogeneous CTC populations of clinical interest independent of their surface marker expression and metastatic propensity to recommend

medication/therapy.

Breast cancer tumor progression is associated with numerous genetic and epigenetic alterations and it can also be detected in CTCs as cfNAs in plasma and serum. The cfNAs might be excellent blood cancer biomarkers, as they may be more informative, specific and accurate than protein biomarkers. In breast cancer patients, tumor cells release ctDNA, mRNA, and microRNA into the blood circulation reflecting the characteristics of the primary tumor and even of micro-metastatic cells, as excellent blood biomarkers. Changes in the levels of circulating nucleic acids have been associated with tumour burden and malignant progression. The analysis of ctDNA is challenging because it is diluted in the background of normal cfDNA. The development of massively parallel sequencing and digital genomic technologies has allowed both screening and validation of genomic alterations. Rigorous studies on genomic characterization of 'liquid biopsies' in breast cancers will need robust assays for analytical validity to demonstrate clinical validity and to become available at the clinical settings. For the last one decade, advances in massively parallel sequencing technologies have enabled the genomic characterization of driver genes and actionable mutations in breast tumour [13]. Any deviation in tumour-derived SNVs or CNA and SVs can be detected in ctDNA from breast cancer patients [14]. These highly sensitive techniques include normal PCR and digital PCR-based tools in addition to sequencing facility [15,16]. Recently, developments in proteomics involving analytical applications of ICP-MS in the area of speciation studies are being welcomed [17]. The most important aspect of ICP-MS is its multi-element capability which can be used for ultra-trace determination of elements in any matrix including BC [18]. The development of the chip is imminent to study the subgroups of distinct biological and phenotypical properties among patients [18]. Especially in BC, further exploration of the biological potential of metastatic and presumably non-metastatic CTCs captured using the microfluidic chip will yield insights into their relevant differences among the subgroups of distinct biological and phenotypical properties and their effects on tumor progression and cancer outcomes [19].

CONCLUSION

In conclusion, owing to the surface antigenic characteristics of BC cells can be detected and treated by complement-dependent cytotoxic antibody assays. The CTCs have shown prognostic relevance in many cancer types due to presence of surface protein expression of disseminated tumor cells. GNPs with their unique surface chemistry, high electron density, strong optical absorption and very low toxicity, have opened up new vistas for rapid detection of several types of cancer including BC. Bioconjugation appears to be crucial method for analysis of antisera and is broadly applicable to imaging and diagnostic purposes. Elevated levels of ctDNA in breast cancer may have diagnostic value. The highly sensitive techniques like digital PCR-based tools and sequencing data will have immense values in the management of the patients.

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