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Nanotheranostic approaches for management of bloodstream bacterial infections

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Abstract

Bloodstream bacterial infections are a serious threat to global public health and economy. The recent figures released by National Center for Health Statistics indicate that more than a million Americans get affected by it each year and the sepsis mortality alone is about 28%-50% Hall et al. (2011).[1] Robust and affordable point-of-care medical technologies are, therefore, urgently needed for rapid decision-making to initiate appropriate line of treatment. Current techniques based on blood culture and serology do not have quick turnaround times or adequate sensitivities for early intervention. Moreover, antimicrobial resistance poses a great challenge in the fight towards effective bacterial infection management. Nanotheranostics is emerging as a novel strategy combining solutions for rapid diagnosis and treatment in a more personalized way. This review highlights the recent advances made in theranosis of bloodstream bacterial infections using different classes of nanomaterials and bioreceptors, and discusses present challenges and future way forward.

Key words: Antibiotics; diagnosis; nanomaterial; pathogen; theranosis; therapy

The term theranosis was first coined in 2002 by, John Funkhouser, the PharmaNetics company president, while defining his company's business strategies for development of diagnostics and its direct relevance to personalized therapy. He defined diagnosis as the "the ability to define a disease state" and theranosis as "the ability to affect therapy or treatment by diagnosis of the disease".[2] Since then, a whole new research area has emerged encompassing different ways by which a single strategy or set of biomolecular systems can be harnessed simultaneously for targeted drug delivery and diagnostic purposes.[3,4] A large thrust to this area has been given by the significant advancements made in the field of nanomaterials – their synthesis, functionalization and assembly for biomedical applications. Optically active nanoparticles (NPs), for instance, can now be routinely prepared in lab for use as biosensing tracers via molecular image tracking and further be combined with controlled on-site release of drugs inside tissues by locally induced changes in environmental parameters (pH, temperature, enzymes, *etc.*).[5,6] Similarly, red blood cell (RBC) micromotors encapsulating anti-cancer drug doxorubicin, quantum dots (QDs), and magnetic nanoparticles (MNPs) have been proposed for cancer treatment in which, the QDs and doxorubicin provide direct fluorescence quantification of the drug loading and MNPs enable magnetic resonance imaging (MRI).[7] This integrated approach of using multifunctional nanomaterials for theranostic applications has opened many possibilities for designing novel platforms that can help combat infectious diseases at an early stage.[8,9]

So far, there are many reviews available on the theranostic approaches of nanomaterials for oncology applications,[9-13] but to our knowledge only a few articles exist on the use of these materials for effective infectious disease management. Infectious diseases, commonly caused by bacterial pathogens, are now the world's leading cause of premature deaths and the third in line after cancer and cardiovascular related mortalities.[14,15] This results in a huge social and financial burden on the governments,

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especially in developing countries, as they struggle to improve sanitation conditions and inequalities in the healthcare ecosystem.[16] The high cost of antibiotic therapy and their poor delivery and management within resource-poor settings, however, still remain outstanding challenges towards fulfilling this mission. Even in developed countries like the US, a substantial number of bacterial borne diseases are recorded in patients admitted to the hospitals.[17] The number of people suspected of septicemia, a severe medical condition most often caused by a bacterial insult in immune suppressed patients, alone exceeds 750,000 annually.[18] Most of these patients are treated in intensive care units (ICUs), constituting 10% of all ICU population. The recent figures released by National Center for Health Statistics indicate that more than a million Americans get affected by it each year and the sepsis mortality alone is about 28-50%. In view of these statistics, it becomes imperative to understand the current challenges in the diagnosis and treatment of bacterial infections and the new strategies that have emerged in the past few years to overcome these challenges.

In this review, we focus on the role of nanomaterials in bacterial theranostics. We discuss the conventional methods available for diagnosis of bacterial infections in a healthcare setting and highlight the associated short and long-term challenges in their adaptability across different diseases and strata of society. This is followed by a review of the different classes of receptor molecules used for targeting bacterial pathogens and the role of various types of NPs serving as efficient carrier agents for these receptors. We also deliberate on the advantages and limitations of using drugs as novel affinity ligands for early diagnosis as part of the broader nanoengineering strategy. Finally towards the end, we summarize our findings and give our perspective on where this advancing and vastly exciting field of nanotheranostics stands today with respect to infectious disease management and how it may progress in the years to come. Besides bacteria, theranostic platforms also exist for parasitic and viral infections but are beyond the scope of this review.[19,20]

Existing methodologies for laboratory diagnosis and therapy of bacterial infections and their challenges

One of the main challenges of pathogen detection at early stages of infection is their low numbers in the clinical specimen. For example, in case of typhoid fever, number of *Salmonella typhi* is approximately 1 to 10 bacteria per milliliter of extracorporeal blood.[21,22] This number is comparable to that of circulating tumor cells (CTCs) in metastatic carcinoma, presenting the same, if not higher, degree of difficulty in their isolation and early identification.[23,24] As a result, a number of different techniques exist that allow direct multiplication of the bacteria or any of the pathogen-associated biomarkers to enhance the sensitivity of detection. The most frequently used method and still considered the gold standard by many is the microbial culture technique due to its direct presentation of results and simplicity of performance.[25] In this approach, the bacteria are exponentially grown into colonies over 1 to 3 days (depending on the bacterial species) and then checked under a microscope and further confirmed by biochemical tests. Similarly, another approach is the polymerase chain reaction (PCR) in which, instead of the whole bacterium, only the target sequence of the genomic DNA of the pathogenic cell is multiplied manifolds.[26,27] PCR is currently one of the most sensitive and rapid methods for detecting bacteria, however, its use for clinical sample diagnosis has been limited due to its cost, high susceptibility to inhibitors and contamination. In addition, PCR assays involve multiple steps critical to its performance including DNA extraction from specimens, PCR amplification, and detection of amplicons, which requires expensive and dedicated resources.[28]

Blood culture is a routinely used diagnostic technique for detection of bacteremia, however, it does not always provide conclusive answers due to various constraints like false negatives (due to prior antibiotic exposure to broad spectrum antibiotics) and contamination of the specimen. This limits the blood culture method sensitivity to no more than 30% to 40%.[29] For these reasons, diagnosis of many diseases is additionally performed via serological testing in which the presence of antibody or host biomarker generated in specific response to the pathogen is measured. For instance, the concentrations of IgG or IgM antibodies can be estimated in sera using bead/cell agglutination or lateral flow assays which are easy to use and can truly work at the point-of-care (POC).[30] The limitations of serological testing are poor sensitivity and late diagnosis as the host-side antibody response takes several days or even weeks after the first appearance of the clinical symptoms. This often delays the initiation of specific therapy, increases the cost and discomfort to the patient, as well as leads to development of drug resistance in the bacterial pathogen.

Although laboratory tests have a great impact on diagnosis, in the absence of sensitive and rapid POC tests, doctors are often forced to make empirical decisions based on clinical symptoms and history of the patient. The empirical therapy prescribed by the physician many a time includes a combination of antibiotics including narrow and broad spectrum drugs, especially in cases of severe bacterial infections.[31,32] Although combination antibiotic treatment has greater immediate outcomes (as compared to monotherapy) due to its synergistic effects and less chances for encountering resistance, its use is also highly controversial. Excessive usage of combinations leads to increased risk of toxicity, super-infection, selection of resistant strains and higher costs.[33] This problem is further compounded by the fact that prescription medicines are readily available over-the-counter in developing nations and people tend to avoid going to a doctor altogether to avoid higher upfront payouts.

One way to increase the sensitivity of detection to ensure timely treatment of infectious diseases is to amplify the signal originating from the low concentration of bacteria, instead of amplifying the target pathogen themselves. This can be done by tagging the pathogen-derived antigens with functional nanomaterials having characteristic optical, chemical or electromagnetic properties. Nanomaterials form great diagnostic probes as they have high surface area per unit volume availability for ligand conjugation which increases the likelihood of target specific binding events getting converted into detectable signals.[34]

Nanomaterials can also be engineered as nanocarriers of medicine increasing the drug's overall therapeutic index and overcoming many associated limitations of conventional drug