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Perspective

Use of biologically synthesized antimicrobial nanoparticles for improving peritoneal dialysis technique: a translational research perspective

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Peritoneal dialysis (PD) is a well-established renal replacement therapy (RRT) for end-stage renal failure (ESRF)[1] and offers certain clear advantages over hemodialysis[2]. However, PD is often associated with a high risk of infection of the intraperitoneal cavity, subcutaneous tunnel and catheter exit site, which may subsequently form microbial biofilms[1]. Generally, a majority of PD patients suffer from bacterial and fungal infections and if the infection(s) is diagnosed timely, they can be resolved by appropriate antibiotic treatment. However, the immune system of ESRF patients continuing on PD may have been compromised and infections are as frequent as once every 10-15 weeks necessitating frequent use of conventional antimicrobial drugs, which may cause emergence of drug resistance. Further as, higher doses of antibiotics are often required for such infections, this may cause intolerable toxicity. Moreover, infections, if correct it as "not resolve and sustain" for a week or more, may lead to infectious peritonitis[1], which severely affects the functioning of the peritoneal membrane, and its resolution may require hospitalization of the patient.

Clinically, treatment of infectious peritonitis involves rapid resolution of infection by eradicating the causative organism(s) and the preservation of peritoneal membrane function. However, in the majority of severe cases, treatment may fail to resolve the condition even after intravenous and intraperitoneal antibiotics and the patients are switched to hemodialysis, either temporarily or permanently[1,3]. Switching to hemodialysis is undesirable because of complications associated with temporary vascular access, reduced patient autonomy and increased medical costs[1,3]. Infectious peritonitis is not only the major cause of technique failure, but also the leading cause of mortality and morbidity in PD patients[1]. Therefore, there is an urgent need to improve the existing PD technique in terms of its efficacy against infections and *in vivo* adequacy during long-term PD; so that, the frequency of PD associated infections could be reduced during prolonged PD and thereof to reduce the traumatic and life-threatening episodes of infectious peritonitis[1]. Practically, this can be achieved through developing infection resistant PD fluid composition which could provide long term protection against a variety of PD associated infections by bacteria, mycobacteria, fungi or viruses. The key requisite to develop such an efficient and novel composition is that the composition should contain some antimicrobial agents with novel mode of action and multiple molecular targets to tackle microbial resistance. Furthermore, these antimicrobial agents should preserve their efficacy and adequacy (i.e. biocompatibility and non-cytotoxicity) during their frequent and long-term use.

Antimicrobial nanoparticles, especially metal (e.g. gold, silver, titanium and bismuth) and metal oxide (e.g. zinc oxide, titanium oxide, etc.) nanoparticles would be of immense interest owing to their exclusive antimicrobial activity against a variety of infections and potential wound healing and anti-inflammatory properties[4–5]. Metallic nanoparticles have been researched extensively in the past and some of their classes have been found to

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be very effective in terms of their antimicrobial and anti-biofilm properties[2]. Mechanistically, these nanoparticles produce their antimicrobial activity through affecting multiple pathways[2]. Thus, many concurrent mutations would have to occur to develop resistance to these nanoparticles[5]. Therefore, antimicrobial formulations based on these nanoparticles could be administered frequently as required to manage recurrent and persistent infections during long-term PD with reduced risk of developing resistance. Studies have demonstrated that naturally occurring bacteria do not develop antimicrobial resistance against metallic nanoparticles[4]; even some of their classes have the potential to eradicate multidrug-resistant infections when these are used in combination with antibiotics[4–5]. Likewise, some classes can limit biofilm formation either independently or in combination with antibiotics[2]. Owing to such broad spectral antimicrobial properties and activity against biofilms and formidable multidrug resistant pathogens, metallic nanoparticles are finding their potential applications as antimicrobial agents and disinfectants to improve several biomedical devices, pharmaceutical products and healthcare interventions including medicines[4–5]. Based on these attributes, the use of metallic nanoparticles can also be envisaged for developing infection resistant composition of PD fluid (as depicted in ***Fig. 1A***). The particular advantage of employing metal based antimicrobial nanoparticles in this translational research endeavor is that these can be filter-sterilized and added directly to the PD fluid for long term storage and prolonged shelf life[2]. Further more, these can easily withstand temperature variations (ranging from 4°C to 50°C, which is generally encountered during transportation and storage of medical products), under which conventional antibiotics may inactivate or degrade. Moreover, the preparation of nanoparticles is cost-effective and relatively simple compared to antibiotics synthesis[4–7].

Metallic nanoparticles of varying sizes, shapes, and properties can be synthesized using variety of chemical and physical methods. However, these methods often lead to the presence of some toxic chemicals adsorbed on the surface and, if are used in pharmaceutical products or biomedical applications, these could produce intolerable toxicity and adverse effects to humans[2]. This is not an issue when it comes to biologically synthesized nanoparticles, i.e. those synthesized from biomaterials derived from microorganisms or plant parts following green chemistry approach[6]. Green synthesis of nanoparticles (using either plant products or microorganisms) is considered as environmentally benign and cost-effective replacement to the toxic chemical and physical methods.

Compared to plant mediated synthesis, the synthesis of nanoparticles using microorganisms is relatively more tedious and time consuming process, as it requires more steps in maintaining cell culture, longer incubation time for intracellular reduction of metal ions and more steps to purify synthesized nanoparticles. On the other hand, plant mediated green synthesis of nanoparticles is relatively simple and provides several clear advantages[2] like (a) extracellular and rapid biosynthesis as water soluble phytochemicals reduce the metal ions in a much shorter time, (b) no need to maintain time-consuming microbial cultures and purification steps as required in microbial mediated biogenic synthesis, (c) preparation is safe to handle and is free from problems arising due to microbial contamination, (d) cost effectiveness as the use of plant extracts reduces the cost incurring in maintaining microbial cultures and to isolate and purify the synthesized nanoparticles in multiple steps, and (e) availability of broad variability of metabolites that may aid in reduction. The generalized flowchart for plant mediated nano-biosynthesis is shown in ***Fig. 1B***.

Studies have shown that biologically synthesized nanoparticles exhibit better biocompatibility and less cytotoxicity compared to their counterparts prepared using chemical or physical methods[2]. Here, I envisage that metal nanoparticles synthesized biologically can also be used to impart infection resistant properties to peritoneal dialysis fluid owing to their relatively low *in vivo* toxicity and higher biocompatibility. A recent study has shown that zinc oxide nanoparticles synthesized biologically exhibit significantly higher biocidal activity against various pathogens when compared to chemically synthesized ZnO nanoparticles[2]. Such preliminary studies suggest that biologically synthesized nanoparticles have huge potential to address future medical concerns. However, before putting these nanoparticles into human healthcare actions, the key step is to rule out their nano-toxicity and adverse effects on long-term exposure. Therefore, efforts are required to evaluate their pharmacology through conducting dose dependent as well as time of exposure dependent *ex vivo* and *in vivo* studies on human cell lines and animal models. After successful evaluation of preclinical efficacy and toxicity, nanoparticles showing favorable *in vivo* pharmacology response can be envisaged to develop infection resistant composition of peritoneal dialysis (PD) fluid. Simply, this will be achieved through adding non-toxic doses of these nanoparticles into different types of PD fluids widely used in clinics and subsequently, evaluating (a) their efficacy against variety of healthcare associated infections, (b) *in vivo* adequacy, and (c) time stability to ensure their long-term

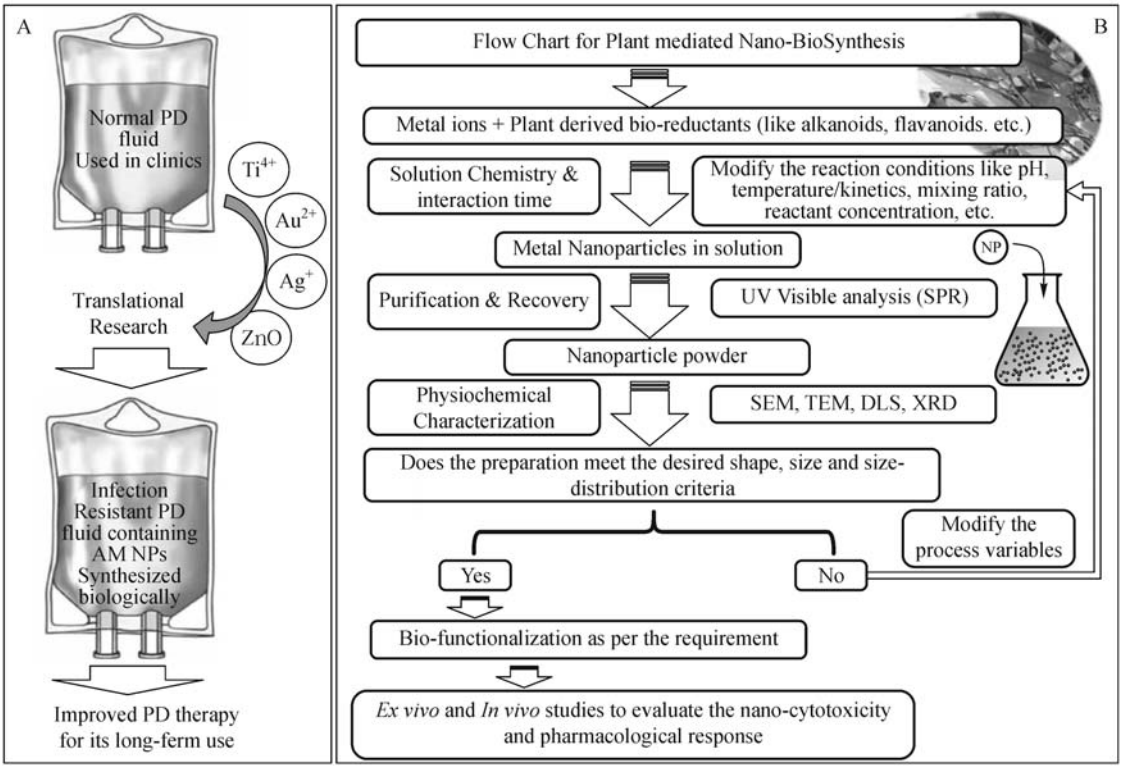

Fig. 1 A: Pictorial illustration for developing infection resistant PD fluid composition through the use antimicrobial nanoparticles (AM-NPs). B: Flowchart denoting the plant-mediated biological synthesis of nanoparticles. The acronyms AM, NPs, PD, UV, SPR, SEM, TEM, DLS, and XRD used in (A) and (B) represent, respectively, anti-microbial, nanoparticles, peritoneal dialysis, ultraviolet, surface plasma resonance, scanning electron microscope, transmission electron microscope, dynamics light scattering and X-ray diffraction.

storage and prolonged shelf life. Strategically, a good start in this direction could be to evaluate the use of nano-sized particles of zinc oxide (ZnO) which is already listed as "generally recognized as safe (GRAS)" by the U.S. Food and Drug Administration (21CFR182.8991). Further more, various studies have shown that ZnO nanoparticles exhibit antimicrobial properties and is also used as food additive for its long-term preservation[2]. Likewise, the use of other antimicrobial nanomaterials safe to human beings (e.g. preferably Copper or Silver oxide NPs) can also be explored in the design of infection resistant PD fluid and further to bring the resulted composition into clinical use through performing meticulous translational research. Important to mention here is that the new PD fluid composition containing non-toxic doses of metallic nanoparticles would be delivered directly into the intraperitoneal cavity, therefore, intraperitoneal uptake of these nanoparticles to other parts of the body and thereof non-specific dissemination may lead to unexpected toxicities, side effects and other complications. Therefore, before putting the new PD fluid composition in clinical use, it would require careful assessment of its pharmacology and pharmacoknietics. In this regard, pharmacometabolomics, an emerging application of metabolomics for deriving early pre-clinical indications of efficacy and toxicity of pharmaceutical products, has huge potential to guide the anticipated translational research endeavors.

Different from metal-based nano-particles, the use of nano-scale antimicrobial materials derived from natural biological substances, including oligo/poly-saccharide based nanoparticles, liposomes, dendrimers, and etc., can also be envisaged in this translational research endeavor. Further, the use of promising antimicrobial nanoparticles in conjunction with novel antibiotic agents can also be explored to manage multidrug resistant pathogens and formation of biofilms during long-term PD. The antibiotics can be added directly into the PD fluid containing antimicrobial nanoparticles at the time of intra-peritoneal instillation. Recently, Dr. Yang's group and their collaborators from IBM Research have co-developed a biodegradable, biocompatible and cost-effective hydrogel that can adapt different shapes and can target variety of bacteria and fungi responsible for healthcare associated infections[8]. The remarkable property of these hydrogels is their ability to target multidrug-resistant biofilms and to

eliminate naturally by the body owing to their biodegradable nature. Therefore, these hydrogels could also serve as useful starting material in this endeavor i.e. to evaluate their clinically safe use for eradicating intraperitoneal, catheter exit-site and subcutaneous tunnel infections which are often caused by microbial adhesion and subsequent biofilm formation following episode(s) of infection.

In conclusion, necessity to improve the PD technology for limiting frequent PD associated infections and possibility to encompass the benefits of antimicrobial nanoparticles synthesized biologically, have been discussed in a translation research perspective. Particularly, the biocompatibility and cytotoxicity of metal based antimicrobial nanoparticles are the key issues to be addressed before putting them into clinical applications. I foresee that this perspective article would definitely appeal some of the biomedical researchers to put their conscience efforts in the direction of developing infection resistant PD fluid composition or nanotechnology based solutions targeting PD related biofilms for its efficient and long-term management.

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