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Nanoscience in the Antibiotics Sphere

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Editorial

The dawn of the antibiotic-era was started with the world's revolutionary invention of Penicillin in the 1940s by the world-leading Scottish scientists, physician, microbiologist, pharmacologist and botanist, Sir Alexander Fleming. After few years, in 1945, for the discovery of penicillin and its curative effect in various infectious diseases, the Nobel Prize in physiology or medicine was awarded jointly to Sir Alexander Fleming, Ernst Boris Chain, and Sir Howard Walter Florey. Since then, the antimicrobial chemotherapy has been an instrumental in mounting of the human life-expectancy. It is beyond the imagination to think of a modern world without antibiotic; for humans, it could be a grim thought leading to a world filled with contagious pathogens. At the beginning, the danger in terms of "antibacterial resistance" to patients came from insufficient dosage, not from uncontrolled consumption and inappropriate usage. However, currently, antibacterial resistance is as if a "global terrorism" which, is resulted due to the invasion in the different pathway by a class of harmful and infectious strains of bacteria to drug molecule, indiscriminate use in agriculture and animal husbandry farms, irregular consumptions, irrational prescribing of antibiotics coupled with poor adherence [1]. The first "superbug" that became resistant to penicillin is *Staphylococcus aureus* in the 1950s and since then the horizontal rise of antibiotic resistance has taken away around 700,000 human lives each year worldwide and it may reach to 10 million per year by 2050 [2]. World Health Organization (WHO) published a list of the most life-threatening multidrug-resistant bacteria (27 February 2017 | GENEVA) to draw the attention for developing new antibiotics in a paramount priority [3]. WHO celebrated World Antibiotic Awareness week, 13-19 November 2017 to raise awareness to the general public, health professionals, governments, farmers, veterinarians, the food and feed industry to promote best practices to reduce the emergence and spread of antibiotic-resistant microbes in both humans and animals. Due to limited development of new resistance-breaking drugs, millions of lives might be endangered in the coming decades. Nonetheless, the antibiotics are continued as empiric agents for combination therapies for invasive infections caused by *Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacteriaceae, Enterococcus faecium, Staphylococcus aureus, Helicobacter pylori, Campylobacter spp., Salmonellae, Neisseria gonorrhoeae, Mycobacterium tuberculosis* bacteria and so on.

For conferring the greatest benefit to mankind, the existing antibiotics could be served as potential candidates in their non-traditional nano-state with a unique mechanistic pathway for the treatment of infections caused by multi-drug resistant (MDR) bacteria. Spurred by the emerging applications of nanoscience and nanotechnology in medicinal field, the reuse of old and/or discarded antibiotics in their nano-state might expedite the revolution of the pharmaceutical industry for the development of therapeutic microbiological applications to prevent the catastrophic consequences of antibiotic resistance [4]. It is obvious and ubiquitous to the scientific community that at the nano-state, molecular and/or atomic level, the most intriguing properties, such as the large surface/volume ratio of the materials produces the unique and well defined physicochemical, pharmacodynamic and pharmacokinetic properties [5]. These unusual and exceptional properties of the nanoparticles are inherently acquired by the effects of ultra-small and controllable quantum size, shapes (spheres, rods, wires, planes, stars, cages, multipods), functionalizable structure and surface charge of the nanomaterials, which make them a suitable candidate for antimicrobial applications. Nanotechnology's assistance for detection, diagnosis, imaging, and therapy assist the clinical benefits for better treatment and/or to reduce the use of antibiotics [6]. Here, it is worthy to mention as instances that the advancement of graphene and metal-based nanosensors/probes/chips promote to facilitate the detection and treatment at an early stage of the disease. Modification of surface properties of the materials, such as the development of mineral-based photocatalyst nanocoating is also praiseworthy for targeting biofilms to inhibit bacterial spread. Nanocoating on the surface of the biomedical objects, such as catheters, implants, contact lenses, and surgical equipment enhances the binding strength either by selectivity and/or specificity towards the target, trap, and

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microorganisms to prohibit the growth of the concerned issues [7]. Magnetic nanoparticles are another type of important candidates for various medical applications related to magnetic resonance imaging (MRI), site-specific drug delivery, labeling and sorting of biological species, food and drug industries and clinical therapy [8].

In addition to these exposures of nanotechnology-based medical devices, the contribution from nanoscience to antibacterial drug development could play a substantial role to reduce or to stop the resistance. The pharmacokinetics and therapeutic index of the drugs can be significantly affected in contrast to the free drug counterparts by transforming the bulk drugs into nanoparticles through physical encapsulation, adsorption, or chemical modification [9]. Using all these simple well-accepted methods, the transformation of old antibiotics into their nanoform rather than development of new antibiotics at the cost of huge investment of time, effort and bucks is wise steps, which directly related to the improvement of serum solubility, the systemic circulation lifetime, sustained and controlled releasing of the drugs, preferentially delivering drugs to the particular tissues and cells of interest, and concurrently delivering multiple therapeutic agents to the same cells for combination therapy. For the delivery of so-called antibiotics as nanodrugs, different biodegradable and biocompatible biopolymers, liposome, dendrimer, hydrogels etc. are already initiated by different groups and found that the advent of nanotechnology has allowed the belittling of the challenging problems of modern medicine and the difficulties in finding alternatives for combating the accelerated emergence of drug-resistant bacterial strains and their ability to form biofilms. The antibacterial resistance arises due to three reasons namely: 1) modification of active site of the target resulting in a reduction in the efficiency of binding of the drug, 2) direct destruction or modification of the antibiotic by enzymes produced by the organism or, 3) efflux of antibiotic from the cell. The advancement of nanotechnology has introduced the several ways in which the bacterial resistance could be diminished or eradicated as there is a possibility to target nanobased-antimicrobial agents to the site of infection, so that higher doses of the drug can be given at the infected site and thereby finding a possibility for overcoming existing resistance mechanisms with fewer harmful effects upon the patient. The working principle of the nanoform of the old antibiotics might be either conventional or nonconventional as the chemical structure at the nanostate may induce mutations in the evolutionary conserved bacterial membrane or disrupt mature biofilms at antibacterial-effective concentrations, therefore reducing the possibility of acquiring resistance.

Modern drug encapsulation methods allow efficient loading of drug molecules inside the nanoparticles by reducing systemic toxicity associated with drugs. Surface area, size, shape, size distribution, and zeta potential are important to determine their cellular uptake and permeability across biological barriers and stability defying the natural aggregation and agglomeration of the nanoparticles. In this context, lipid nanoparticles are the attractive alternative drug vehicles due to their biocompatibility, versatility, and their ability to target biofilm infections. While, one more contemporarily developed polymeric nanoparticles-derived drug carrier eradicate microorganisms either by releasing antibiotics, antimicrobial peptides, and antimicrobial agents or by contact-killing cationic surfaces. In this regard, it is necessary to know that a few nano-based products are under clinical trials or permitted to be used for clinical drug delivery and bio-imaging to implantable biomaterials and medical devices. Despite these potential deliberations, the development of new antimicrobials and antimicrobial vaccines is still comparably insignificant.

With economic and technological benefits, the challenges associated with the environmental, occupational, health and safety risk of nanomaterials and nanotechnologies are a global concern [10]. Several research initiatives and thorough investigations are required to ensure the toxicity, hazardous and environmental impact of nanomaterials on mankind and environment. Year after year, the outweighing and overlooking the potential negative effects, unsafe characteristics and properties of nanomaterials became the regular practice because of their commercial benefits. To deal with the potentially dangerous health risk, the most important is to control the size of the nanoparticle as there is probability to cross the central nervous system (CNS), to enter and translocate within, and damage living organisms due to their small size, which allows them to penetrate physiological barriers, and travel within the circulatory systems of a host. Meanwhile, nanomaterials and nanotechnologies are constantly supporting the pharmaceutical sectors to enhance their global competency; their increased rate of success also demands to ensure their safety. Although, nanomaterials are used in different pharmaceutical sectors, but the regulatory framework and structure of the clinical approval process is in progress and not yet matured to ensure that sponsors demonstrate adequate safety and efficacy before a product is launched in the market. The nanoscale in one or more dimensions and the form of the particles can easily aggregate and agglomerate due to their inherent inter-particle bond energies in terms of weak van der Waals forces. Several nations have now started to provide a defined regulatory framework for the application of nanotechnology in healthcare, highlighting advantages and disadvantages for the patients. In the recent past around 2011, the European Commission has adopted a recommendation on the definition according to which 'nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions are in the size ranging from 1–100 nm. According to the US decision-making concerning regulation, some definitions apply the size range to two or more dimensions–using either external or internal structures as units to be measured. Furthermore, the size-specific properties of the nanoparticle limited the use of currently available *in vitro* experiments, and the standardized definition for NP dosage in mass, number, surface area, and biological samples (e.g., blood, urine, and inside organs) are still not clear. According to WHO, the growing number of infections, such as pneumonia, tuberculosis, gonorrhea, and salmonellosis, MRSA infections and just to name a few are becoming harder to treat as the antibiotics used to treat them become less effective.

The old class of clinically used antibiotics like penicillins, cephalosporins, macrolides, fluoroquinolones, sulfonamides, tetracyclines, aminoglycosides and others like rifamycins, vancomycin etc. are now facing resistant problem in addition to another dose-related toxicity problem. Of these, aminoglycosides, which are one of the naturally occurring, less expensive and easily available important and potent broad-spectrum antibiotics with high potency, have been using for the treatment of severe infections of the abdomen and urinary tract, as well as bacteremia, endocarditis, and tuberculosis etc.

Recently, the high bacterial resistance rates to naturally occurring aminoglycosides exhibited by Gram-negative and Gram-positive bacteria attributed the selective urges to academia and pharmaceutical

industries for the development of modified aminoglycosides to control the infections caused by new and/or resistant strains of bacteria [11]. However, it is a belief that the development of modified aminoglycosides will not suffice to control the infections caused by new and/or resistant strains of bacteria but at the same time, we have to be more careful regarding the usage, consumption, doctor's prescription and just to name a few to fight against this global threats. For a synthetic medicinal chemist, it is an understanding that the modification of the old version of aminoglycoside-based drug molecules is one of the best ways to combat with the impact of concordant effects of uncontrolled usage, consumption, doctor's order of antibiotics.

Recently, research and development for newer antibiotics have dropped drastically over the years, which mean it will take even longer to get new forms of antibiotics than ever before. While ease of modification and availability of the naturally occurring aminoglycosides stimulated the synthetic chemist to engage them for the development of the newly modified aminoglycoside derivatives with high potency to work in disguise against many new and resistant strains of the harmful bacteria. Thus, many factors, which could influence the future role of aminoglycosides as antibiotic, will include economic, administrative, and space pressures to restrict the number of antibiotics available for clinical purposes, the development of novel antibiotics at the cost of huge investment, the utility of combination therapies, the comparative toxicities of new antimicrobial regimens, and considerations of cost restraint. However, many efforts towards the synthesis of novel aminoglycoside derivatives through modification have demonstrated that these modified versions have a potential for reversal of resistance with abrogated toxicity and new activities to treat HIV-1 and even human genetic disorders. It is not the end for aminoglycosides, but rather, the challenges faced by researchers have led to ingenuity and a change in how we view this class of compounds, a renaissance and also for the other antibiotics and in this cases nanoscience could help to resist the multidrug drug resistance in addition to the reduce of dose-related nephro- and ototoxicity.

In addition to the issues like industrial preparation, stability, safety, etc. for the nanoscience in the sphere of antibiotics, but the knowledge gained in diagnosis, targeted drug delivery, medical devices, energy, and packaging, may over time be transferred, or provide spillovers to antimicrobial drug development applications as well. If the academic, industrial, and society join their hands together, then we will be able to fight against the life-threatening issues, such as antibacterial resistance and biofilm formation with the help of nanoscience and nanotechnology in the sphere of antibiotics. I am of the opinion that the step of nanotransformation of old and discarded antibiotics shall overcome the intrinsic resistance and biofilm formation of bacteria could join in the fray to deal with the increased emergence of the public health concern and today's effort might become a symbol and beacon of hope in future for the world.

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