THE USE OF NANOTECHNOLOGY FOR THE DETECTION AND TREATMENT OF CHOLERA.

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RESEARCH PAPER BASED ON PATHOLOGY LECTURES AT MEDLINK/VETLINK 2010

Abstract

Cholera is a bacterial infection (Figure 1), causing diarrhoea and de-hydration, which can be de-habilitating, and often fatal with more than 100 serotypes of which only two affect humans. Evident mostly in areas without safe drinking water, it often appears after a major natural disaster or in overcrowded conditions. However, a vaccine is available for only one serotype. The current diagnostic test which is expensive and slow is performed on stool samples which need to be examined under laboratory conditions. Consequently, by the time it is confirmed as Cholera, it is already on its way to becoming an epidemic. A new test utilising nanotechnology could be the answer. It is relatively cheap to produce and can be used at the suspected site of infection and provides quicker results allowing immediate action to be taken.

Introduction

"Living organisms are naturally -existing, fabulously complex systems of molecular nanotechnology." - Dr. Gregory Fahy.

As this quote suggests; living organisms consist of complex systems of molecular nanotechnology, therefore can we use nanotechnology to treat living organisms today? A new generation, more research and more discoveries. You may ask what scientists first consider when researching new cures and detection devices for diseases in both humans and animals. Here could be the answer; nanotechnology. Nanotechnology involves manipulating properties and structures at the nanoscale; 1×10-9 m. In comparison, the width of a human hair is 200,000 nm. Nano comes from the Greek word "nanos"- dwarf.

Nanoparticles have already been used in products such as cosmetics and sunscreens, and are now being applied to medicine. They have succeeded in providing effective applications such as drug delivery systems, cancer detectors and disease treatments.

Nanotechnology has provided detection appliances and possible treatments for Alzheimer's disease. Dr. Alois Alzheimer a German neurologist discovered Alzheimer's disease in 1906. It was not until the 1960's that Alzheimer's disease was acknowledged as a disease, and research is still ongoing today to find a suitable cure. Although further research is needed, currently funding is limited and most of the funding is spent on other diseases e.g. Cancer.

As the world's population passes 9 billion, every day there are an extra 200,000 mouths to sustain and keep healthy. To tackle the global population growth, we must be more radical in our thinking. Technology to produce much higher yields is currently scientifically possible, but has not yet been applied. New technology to combat disease epidemics could be developed, and again is not being applied. Nanosensor networks to continuously monitor the health of plants or animals or even humans in the future, perhaps?

Now its time to think about how we can apply nanotechnology to diagnosing or detecting some of the worlds many diseases. Recent figures from the World Health Organisation (WHO) estimate 3 to 5 million cases of Cholera every year with 100,000 to 120,000 deaths. This disease normally follows a major natural disaster, extreme overcrowding and poverty or major population displacements. The current test to detect cholera is expensive and slow. Recent research suggests nanotechnology could hold the answer.

Figure 1

Figure 2

Discussion

Norio Taniguchi first used the term “Nanotechnology” in 1974; a researcher at the University of Tokyo referring to the ability of engineering materials at nanoscale. Nanotechnology has been present in nature since the beginning. The nanoscale layers on the structure of butterfly wings which reflect light and give them such wonderful colours. The gecko hanging upside down on a sheer surface, able to because of the millions of nanohairs on each toe.

Nanotechnology can be used in the production of nanomaterials from thin waterproof fabrics, silicon nanowires for transfer and storage of data, nanoelectrics such as sensors or quantum dots and nanotubes replacing cathode rays in televisions, nano-biotechnology for drug delivery, tissue engineering and bio-nanosensors. Nanotechnology encompasses three main fields, biomedicine, engineering and technology with applications for its use unlimited except by our capabilities.

University of Bath scientists working jointly with Frenchay Hospital in Bristol, teams across Europe and Australia are developing a revolutionary advanced wound dressing for burns victims both in the domestic situation and within the military field. This wound dressing is covered with nanocapsules containing antibiotics, being triggered only by disease causing bacteria producing toxins. These toxins break open the nanocapsules, containing not only the antibiotics but also a dye that changes colour to act as an early warning system of the presence of infection. The European Commission is already funding a 4.5 million euro project with the Max-Planck-Institute for Polymer Research Germany, which will develop a prototype dressing over the next four years.

Albert Einstein College of Medicine of Yeshira University are currently trying a new approach to treating antibiotic resistant bacteria. They have nanoparticles smaller than a pollen grain, carrying nitric oxide gas that release their cargo, penetrating deep into the skin after being applied as a topical treatment. The nitric oxide helps the body’s natural immune system fight infections. This treatment is even effective at fighting methicillian-resistant Staphanreus and MRSA; the lethal super bug plaguing our hospitals. Nitric oxide is a very short-lived gas produced naturally by our bodies, it aids to kill bacteria, increase blood flow by dilating blood vessels and heal wounds. With nanoparticles treatment can be delivered to a specific target with an effective sustained dose revolutionising medical treatments.

Envisage nanorobots (Figure 2) at sizes between 0.5 to 3 microns, which are capable of travelling through the body without causing any damage. These nanorobots were first introduced by Richard Feynman, an American physicist and Noble Peace Prize winner. This has given medicine the gateway to successful treatments and diagnoses, with advantages such as faster recovery rates, as the nanorobot only attacks the affected area. With further research, nanorobots could be used to treat a variety of diseases.

The two types of Cholera bacteria that affect humans are V. cholerae 01 and V. cholera 0139. V. Cholerae 0139 contains two subtypes, Classical and EL Tor.

You can contract Cholera by drinking infected water or eating food prepared with infected water e.g. fresh green salad leaves or shellfish. The bacteria multiply within the intestines and within 24 to 48 hours the symptoms will appear. symptoms can be mild but one in twenty cases will be severe. The specific symptoms are large amounts of watery diarrhoea, vomiting and muscle cramps. As a consequence, when the fluid is lost other symptoms occur, including weaknesses, increased heart rate, reduced urine production, coma and death. Cholera treatment will reduce the chance of serious complications but the outbreak is usually severe before the treatment is available.

Doxycycline tablets along with fluid replacement therapy are the normal treatments and costs 60p a day per person for the antibiotics alone. To prevent you contracting Cholera you need to take the tablets 2 weeks prior the chance of being exposed to the bacteria and 4 weeks afterwards, with the possible side effects of nausea, drowsiness and general sickness. The problem being that you are not issued with a two-week warning of a natural disaster to allow you to take preventive medicine.

There is also a vaccine available called Dukoral which requires two doses, one week apart and at least a week after the second dose to become effective against the Cholera bacteria. Again, you don’t get a two week notice issued with natural disasters.

We suggest the answer could be a regular sampling of the available water sources following disruption to normal water supplies, utilising the speed, ease and efficiency of the University of Central Florida nanotechnology based test.

This test allows aid workers to conduct an on-site test and continue to monitor the water quality. This is likely to be a preventative and hence cheaper measure.

The Cholera toxin could be detected and the contaminated source restricted. “It’s really quite amazing” said the University of Central Florida assistant professor J. Manuel Perez, “It means we have a quicker diagnostic tool using a simple and relatively cheap sugar- nanoparticle combination” The technique developed by the University of Central Florida uses the sugar dextran coated with iron oxide nanoparticles. The nanoparticles are then added to a water sample and because the dextran looks similar to the Cholera toxin receptor, the Cholera toxin, if present, will bind to the nanoparticles; dextran. This is because dextran looks similar to the Cholera toxin receptor ganglioside found on the cell’s surface in the victim’s gut.

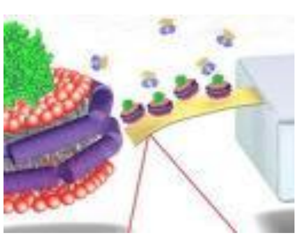

Figure 3

Iron oxide nanoparticles are able to bind to specific locations whilst covalently bonded to an appropriate ligand (Figure 3). Changes in the solution's spin-spin relaxation times allow this binding to be observed through measuring the magnetic relaxation. Ganglioside; the cellular Cholera toxin B receptor is present with a pentasaccharide moiety made up of galactose and glucose units. The scientists carrying out the research foresaw the probability that the cellular Cholera toxin B would realise that the carbohydrate-conjugated iron oxide nanoparticles are ganglioside copies and visible alterations will be seen in the relaxation times. These visible changes from the magnetic relaxation experiments proved the scientist's theory that the cellular Cholera toxin B would form with the galactose-conjugated nanoparticles. This theory was supported with surface plasmon resonance studies, including the free nanoparticle conjugated galactose molecule. It was then possible to use the galactose-conjugated nanoparticles in cellular Cholera toxin B sensors, achieving an impressive detection limit of 40 pM. This led to the discovery that the cellular Cholera toxin B, also bound with dextran-coated nanoparticles and again surface plasmon resonance proved this interaction. Further experiments were able to widen the theory by utilising the use of dextran-coated nanoparticles in cellular Cholera toxin B sensors. Also, it was evident that dextran can prevent the internalization of the cellular Cholera toxin B into ganglioside-expressing cells. This research confirms that magnetic nanoparticles conjugate and magnetic relaxation detection can be a swift and straightforward way of identifying and targeting ligands through molecular copying.

The technique is likely to be cheaper than those currently on the market, as these nanoparticles are cheaper to make in large quantities as both dextran and iron oxide are commonly used in other medical applications. Also, the detection instruments are in some cases the size of desktop computers and could be developed into handheld mobile devices to be used in the field.

Another development in nanotechnology regarding the detection of Cholera has been nanomechanical sensors. Molecular biologists developed a synthetic membrane model called Nanodisc (Figure 4). This is a membrane scaffold protein belt surrounding a self-assembled phospholipid bilayer disc of about a 10 nm diameter. Hydrophobic and amphipathic molecules are made soluble by nanodiscs, hence making possible a new range of applications for in vivo delivery of therapeutic diagnostic and imaging agents as well as for in vitro drug delivery. The liposomes traditionally used for solubilising membranes associated macromolecules form large complexes which are heterogeneous, distort the surface phenomena by being unstable. By contrast, the nanodiscs with controlled stoichiometry of the contained protein makes observation and analyzing easier. Soo-Hyun Tark, a Postdoctoral fellow in the Department of Materials Science and Engineering at North-western University says, "We envision such a Nanodisc based detection approach may find significant applications in drug discovery and pathogen monitoring"

Figure 4

The Cholera bacteria has been identified in countries where it is endemic living in aquatic ecosystems. It is here able to adapt to changes in its environment by moving from a free floating “planktonic” form to slimy “biofilms”. The biofilm makes the Cholera bacteria much more resistant to antibiotics and disinfectants than when it is in its free-floating form. Established methods of control are water chlorination, though this may not be as effective. Future nanotechnology could be implemented by using medical nanodiscs to work alongside our immune system to identify and attach themselves to the cholera bacteria enabling it to be disabled completely. Nanomachines could be used by being placed in the water supply itself to identify and destroy any Cholera bacteria present before the bacterium was able to affect humans.

Dextran could also aid in the treatment of people already infected with Cholera. Dextran’s molecular mimicry of the body’s cells, to which Cholera toxin binds itself, acts as a competitive inhibitor, distracting much of the toxin from the body’s cells. Thereby decreasing the number of infected cells, reducing recovery rates.

The development of nanostructures that are able to encapsulate drugs and protect them from internal degradation, and that are also able to target their delivery to a specific area of the body to release the incorporated drug at a sustained and continuous rate. Thus, being able to penetrate into tissues allowing efficient drug release. These nanostructures maybe the answer for treating Cholera quickly; increasing the patients recovery rate.

Scripps Research Institute in San Diego have already developed nanotubes formed by peptides (Figure 5) that attack bacteria by piercing holes in their membranes. By using different types of peptides, they have designed nanotubes that selectively seek out and invade bacterial membranes without harming the body’s cells. These nano-bioagents should be less prone to bacterial resistance as the disease-invading bacteria would have to alter its whole membrane dramatically to become resistant. These peptide nanotubes are also resistant to proteases that digest some antibiotics, solving a problem when designing antibiotic agents.

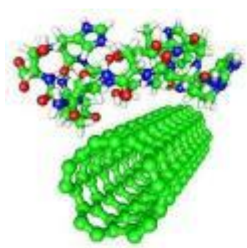

Figure 5

Conclusion

The “would be” benefits of nanotechnology are huge but so is the potential to misuse it. Chemical weapons produced from nanoparticles could be even more harmful due to the fact that the smaller a particle, the greater its impact either positively or negatively. Research shows increased toxicity on some nanoparticles due to their increased surface area. Carbon nanotubes have been shown to induce tumours in studies on laboratory animals. Also, nanoparticles of copper, titanium oxide, silicon oxide and cobalt have a toxic and inflammatory effect on certain cells.

A study in 2005 at Rice University confirmed that certain nanoparticles are bactericidal and as bacteria are the foundations of many ecosystems, their misuse could be disastrous.

The safety of this technology and its application on plants, animals and humans have the potential for its destructive use. All of the above needs careful monitoring to reduce the risks and maximize the benefits.

At an Oxford farming conference earlier this year, Mr. Clark told delegates, “Scientists need to be more careful about promoting their science and they need media training so they can manage the way their science is promoted. All too often scientists are lulled by the media into promoting the bizarre, talking about jelly fish genes and genes from spiders being incorporated into plants and animals while failing to explain any benefits… They use inappropriate language, concentrate too much on the science without thinking about benefits, and end up falling into the trap of scaring the general public”

Cholera is an endemic in many countries but following flooding, or earthquakes, pollution of water sources occur and not long afterwards, there is a Cholera outbreak.

Developing countries do not have the resources to fund a blanket vaccination programme to protect their population and rely on international aid, which is often delayed, mismanaged or simply unavailable at the right time or place. This simplified, cost effective test, utilising nanoparticles could save thousands of lives and allow the funds to be spent on alternative aid or relief.

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