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Review

Glance at potential future combating of diseases: Bioengineered antimicrobial organisms

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The incidence of diseases is on the surge as exemplified by the recent occurrence in West Africa of Ebola Virus (EBOV) and increase of Zika Virus in Brazil. These pathogens have evolved strategies to evade the human immune system and thus continue to be globally important human pathogens. Bioengineering capabilities are on the increase with rapid advances in synthetic biology and allied technologies (nanobiotechnology, nanotechnology, OMICs technologies, and genetic engineering) which bring potential future prospects in combating disease causing agents using the knowledge of pathogenesis of these disease causing agents. This paper specifically takes a forward looking approach in proposing a potential future use of bioengineering technologies to combat disease causing pathogens as exemplified by Human Immunodeficiency Virus (HIV), Ebola Virus (EBOV), and *Mycobacterium tuberculosis* through the design, building and testing of synthetic bioengineered minimal genomes with pathogen neutralising capabilities and pathogen detection sensitivity similar to whole cell based biosensors.

Key words: Tuberculosis, Ebola, AIDS, synthetic biology, omics, biosensors, nanotechnology

INTRODUCTION

Disease pathogens have been the greatest killers throughout evolution and are expected to have exerted selective pressure on genes involved in host-pathogen interactions (Ortiz et al., 2009). Nearly 35 million human beings globally are infected with Human Immuno-deficiency Virus (HIV) which causes Acquired Immunodeficiency Syndrome (AIDS) (Mann and Ndung'u, 2015; Bharaj and Chahar, 2015). The HIV continues to be a major global public health issue, with a mortality of more than 1.2 million from HIV-related causes globally and approximately 2.0 million people becoming newly infected with HIV in 2014 globally (WHO, 2016). Tuberculosis (TB) is a top infectious disease killer worldwide with, 9.6 million people falling ill with TB and 1.5 million deaths from the disease in 2014 (WHO, 2016). Since March 2014, West Africa experienced the largest outbreak of Ebola in history with 28639 cases and 11316 deaths by 31 January, 2016 (WHO, 2016) whilst an increase in incidence of Zika Virus (ZIKV) which maybe linked to congenital microencephaly has been reported in

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many countries including Brazil, Colombia, El Salvador, French Guiana, Guatemala, Haiti, Honduras Martinique, Mexico, Panama, Paraguay, Suriname, Venezuela, and the Commonwealth of Puerto Rico (WHO, 2016; Schumaker, 2016), and the World Health Organisation declared the disease a public health emergency of international concern (Pearson, 2016). New cases of ZIKV have been reported in United States of America, Denmark, Finland, Portugal, Germany and Portugal (Schumaker, 2016).

The pathogen is defined as a microbe that can cause damage in a susceptible host where pathogenecity is determined by the outcome of the microbe-host factors interaction (Pirofski and Casadevall, 2012). These pathogens such as *Mycobacterium tuberculosis*, Ebola Virus (EBOV), HIV and ZIKV have developed stealth and subtlety that have allowed them to thrive even in the face of modern medicine (Cambier et al., 2014). Future progress in bioengineering technologies may combat effectively the stealth and subtlety that infectious disease pathogens have evolved through the development of a bioengineered antimicrobial organism.

BIOENGINEERING TECHNOLOGIES

The development of advanced bioengineering technologies which can be summarily defined as follows maybe the backbone of emergence of novel ways to combat disease pathogens: nanotechnology is the design (Cheng et al., 2015; Goldup, 2015), the manipulation, the building, the production and the application, by controlling the shape and size, of the properties (responses) and functionality of structures, devices and systems of the order of less than 100 nm (Drexler, 1991; Fakruddin et al., 2012). Biotechnology is the use of living organisms or their parts or processes to the benefit of human – kind. The integration of biomolecules with metallic or semiconductor nanoparticles or carbon nanotubes yields new hybrid nanostructures of unique features that combine the properties of the biomolecules and of the nano-elements and results in a confluence of nanotechnology and biological processes (Nanobiotechnology) (Logothetidis, 2012). 'OMICs' is a powerful group of molecular based technologies that characteristically end with the suffix 'omics' which include genomics (DNA- what can happen), transcriptomics (RNA-what appears to happen), proteomics (proteins-what makes it happen), metabolomics (metabolites-what has happened) (Horgan and Kenny, 2011; Barh et al., 2013; Bogyo and Rudd, 2013; Ge et al., 2013). Omics technologies are able to decipher what is happening in a control standard environment in comparison to a stressed tester environment such as diseased and non-diseased environments. Genetic engineering is introgression of a foreign (non-species) gene into a species using molecular based technology.

Synthetic biology is an emerging bioengineering discipline that attempts to design and rewire biological components, so as to achieve new functions in a robust and predictable manner (Agustín and Isalan, 2014). The aim of synthetic biology is to simplify the process of designing, constructing and modifying complex biological systems (Patron et al., 2015). Synthetic biology treats biological organisms as a new technological medium with a unique set of characteristics, such as the ability to replicate, self-repair and evolve and a proposed community based information exchange standard is proposed for the evolution of synthetic biology in the form of the Synthetic Biology Open Language data standard (Galdzicki et al., 2014). Development of such standards (Patron et al., 2015) may facilitate the needed interaction of synthetic biology, nanotechnology, nanobiotechnology, bioinformatics, OMICS technologies and genetic engineering for the potential development of the bioengineered antimicrobial organisms.

Development of the bioengineered interventions to combat disease pathogens requires an in-depth knowledge of pathogenesis and immunity of which OMICs technologies potentially are able to characterise the pathogen whilst synthetic biology, nanobiotechnology and bioinformatics may be employed in designing the bioengineered antimicrobial organism using the information gathered from omics technologies studies. Building of the bioengineered antimicrobial organism may be through synthetic biology, genetic engineering and nanobiotechnology leading to testing (laboratory, then animal trials, then human clinical trials) of the bioengineered antimicrobial organism.

A glance at future prospects of bioengineered antimicrobial organisms

When a pathogen passes the human species skin which presents a first line of defense against infectious agents through inhalation, ingestion, wound or injection the human body then uses natural or innate immune mechanisms where human cells and the chemicals they produce seek out, identify and eliminate the pathogen (Medzhitov, 2000). If the pathogen has mechanisms to evade or suppress these natural immune mechanisms such as encapsulated bacteria which have a polysaccharide coat that prevents phagocytic cells from identifying them and thereby avoid immediate elimination by the innate immune system of the host, then an acquired immune reaction specific to the pathogen is initiated which involves antibodies and cell mediated responses (Pirofski and Casadevall, 2012; Medzhitov, 2000; Siegrist, 2013). This passively acquired immunity results in swift elimination of the pathogen upon unintentional re-exposure.

Intentional exposure to the pathogen or its components through vaccination is known as actively acquired

immunity. Vaccines interact with the immune system and often produce an immune response similar to that produced by the natural infection, but they mostly do not subject the recipient to clinical disease symptoms and potential disease complications (CDC, 2015). The vaccines that are produced can be in the form of live attenuated pathogen (e.g. Mumps, Polio Sabin, Yellow Fever), virus-like particles (e.g. Papillomavirus), killed subunit (e.g. Influenza), killed virus (e.g. Hepatitis A, Rabies) and viral component such as polysaccharide/ protein (e.g. Pneumococcal, Pertussis) (Siegrist, 2013) which result in long-term protection that requires the persistence of vaccine antibodies and/ or the generation of immune memory cells capable of rapid and effective reactivation upon subsequent exposure to the pathogen (Siegrist, 2013).

Recombinant vaccines are produced by genetic engineering technology to produce vaccine antigens such as hepatitis B surface antigen or human papillomavirus (HPV) capsid protein or live Typhoid vaccine (Ty21a) which is *Salmonella typhi* bacteria that have been genetically modified to be non-pathogenic (Siegrist, 2013; CDC, 2015; Plotkin, 2003). A bioengineered antimicrobial organism is proposed to be based on the live recombinant vaccine line but in addition have capabilities developed from synthetic biology, nanotechnology, nanobiotechnology, genetic engineering, OMICs technologies to combat the pathogen.

A glance at the feasibility of developing the bioengineered antimicrobial organism

The evolution of the three species domains; Eucarya, Bacteria and Archaea on the Planet Earth from a progenitor cell is premised on mutations (genetic modification) occurring over the eons of time (geological time scale). The change in the genome brought about by mutation (original source of variation or new alleles naturally) would occasionally result in a new phenotype which would be acted upon by micro-evolutionary forces such as genetic drift, natural selection and migration resulting in adaptations of genomes to particular habitats. This process was accomplished naturally without any synthetic genetic modification.

The coming on board of bioengineering technologies such as synthetic biology, nanobiotechnology and genetic engineering have resulted in humankind having the capability to introduce non-natural genetic modifications at a low percentage of the genome such as in genetically modified organisms and at a high percentage of the genome such as in synthetic biology engineered organisms. These modifications can be taken as human derived, designed ‘mutations.’ Thus, the design, synthesis and assembly of the 1.08 mega base pair *Mycoplasma mycoides* JCVI-syn 1.0 genome and its transplantation into a *M. capricolum* recipient cell to create new *M*. *mycoides* cells that are controlled only by the synthetic chromosome (Gibson et al., 2010) can be taken as a genome-wide synthetic biology induced mutation of *M. capricolum* which is at a large scale because it replaced the *M. capricolum* genome apart from the other sequences acquired during the building process. Thus, it is possible to derive a bioengineered organism with widespread changes to its naturally derived species genome. In other words, an artificially, extensively ‘mutated’ genome is expected for the bioengineered antimicrobial organism or a completely novel designed and synthesized genome.

A whole cell biosensor typically consists of two critical components: a bioreporter strain that has a promoter responsible for sensing or interacting with the target analyte fused to a reporter gene responsible for generation of the detectable signal (Ripp et al., 2010) such as the *Saccharomyces cerevisiae* BLYES *lux*CDABE bioreporter which produces bioluminescence in the presence of estrogenic chemicals. The concept of a whole cell based biosensor was modified to produce a bioengineered *Escherichia coli* microbe that sensed and eradicated *Pseudomonas aeruginosa* which is a human pathogen (Saeidi et al., 2011). This was achieved through replacing the concept of reporter gene in the whole cell biosensor system to a synthetic genetic system that senses and then elicits production of pyocin which is toxic to *P. aeruginosa*. The engineered *E. coli* was able to sense and kill planktonic *P. aeruginosa*, shown by 99% reduction in the viable cells (Saeidi et al., 2011). Thus, it is envisaged that a bioengineered antimicrobial organism would have synthetic biology derived capabilities to neutralize the pathogen.

One of the aims of the bioengineering technology is to engineer biological systems that perform novel functions that do not exist in nature, with reusable, standard interchangeable biological parts such as the BioBrick assembly standards (Endy, 2005; Canton et al., 2008). However, the complexity of natural occurring organisms makes it imperative to have the bioengineered antimicrobial organism designed and built using the minimal cellular genome concept. A minimal synthetic genome of *M. mycoides* JCVI-syn1.0 comprising 473 genes in 531 kilobase pairs making it the smallest genome of any autonomously replicating cell was successfully designed, built and tested for viability (Hutchison III et al., 2016). The method used to identify the essential genes was transposon mutagenesis. A minimal genome has the advantage of less complexity and potentially allows bioengineering of specific novel functions to be designed into the minimal genome.

Thus, a bioengineered antimicrobial organism is not only proposed to be based on the live recombinant vaccine line but also on the minimal genome model with pathogen site tagging incorporated and pathogen neutralizing capabilities developed from bioengineering technologies such as synthetic biology, nanotechnology,

nanobiotechnology and genetic engineering.

A GLANCE AT THE FUTURE PROSPECTS OF BIOENGINEERED ANTI-HIV AGENT

Most drug therapies specifically target HIV proteins, with infection and replication involving about 24 processed HIV proteins (Sargeant et al., 2014). With the introduction of combination antiretroviral therapy in 1996, HIV-1 infection became treatable but not curable (Abbas et al., 2015). To date only one candidate recombinant HIV-1 (*env-gag-protease*)-canarypox vector prime and a recombinant gp120 plus aluminum boost vaccine has significantly reduced acquisition, at a limited efficacy of 31% but without delaying disease progression in vaccinated individuals (Mann and Ndung'u, 2015).

The HIV is associated with continued activation of the immune system which is relatively stable over time and this is known as the driving force behind $CD4^+$ T cell depletion and progression to AIDS with the new notion that levels of chronic immune activation predict the progression to AIDS independently from viral loads or $CD4^+$ T lymphocyte counts (Bharaj and Chahar, 2015; Pirofski and Casadevall, 2012; Coffin and Swanstrom, 2013; Claiborne et al., 2015). The immune activation is most likely to be a significant contributor in the initial establishment and maintenance of the viral reservoir which continually provide a constant trigger to the immune system and thus low level activation persists (Bharaj and Chahar, 2015).

Potential development of Anti-HIV line 1 (non immunogenic constructs and neutralizing antibodies)

Future advances in bioengineering technologies can enable the designing, building and testing of a bioengineered antimicrobial therapeutic agent HIV line 1 that is an HIV-like particle but has non-immunogenic constructs and is able to enter these currently incompletely deciphered viral reservoirs where the infected cells have greater half-lives estimated at ~ 6 months in comparison to the infected cells with ~ 1-2 days or ~ 2 weeks half-lives (Coffin and Swanstrom, 2013) and use the cell machinery to produce HIV antiviral compounds or proteins such as broadly neutralizing antibodies.

Potential development of Anti-HIV line 2 (dummy HIV – 1 proviral DNA)

A recent vaccine approach is to develop virus like particles (VLP) with the non-functional *Env* removed from the surface by enzyme digestion (Mann and Ndung'u, 2015). This VLP approach could be the baseline in the developing of the antimicrobial therapeutic agent HIV line 2 that is bioengineered to elicit the production of dummy HIV-1 proviral DNA. The production of dummy HIV-1 proviral DNA by the therapeutic agent would act as competition to the genuine deadly HIV for integration into the host chromatin and thus reduce the population of cells comprising the 'real' latent reservoir as part of the cells in the latent reservoirs would contain the non-functional dummy HIV-1 proviral DNA.

Potential development of Anti-HIV line 3 (increased precision)

Recently there has been success in using zinc fingers nucleases to delete the CCR5 HIV receptor in white blood cells, which is a potential functional cure for HIV patients (Tebas et al., 2014). However, controlling possible off-target effects may be essential in the safety and success of such an approach in the HIV-1 pathogen and human host interactions. A bioengineered antimicrobial therapeutic agent HIV line 3 could build on this aspect by increased precision on rendering the CCR5 HIV receptor non-functional using bioinformatics tools.

Potential development of Anti-HIV line 4 (successful macrophage entry)

The combination of protease inhibitors and reverse transcriptase inhibitors has been shown to be a powerful therapeutic tool to fight HIV infection (Abbas et al., 2015). However, these therapies are found to be several folds lower in macrophages and this is reported to be due to the P-glycoprotein transporter which limits the availability and absorption of these drugs (Robillard et al., 2014). Future advances in bioengineering technologies may potentially enable the development of therapeutic agent HIV line 4 to possess surface receptors that allow entry into the macrophages where it would elicit production of broadly HIV neutralizing proteins which would potentially address the aforementioned challenge faced by the combination therapy of protease inhibitors and reverse transcriptase inhibitors.

Potential development of Anti-HIV line 5 (gut surface maintenance)

The gut immune system is considered the largest single immunologic organ in the body (Lackner et al., 2012). Most (~95% of the body total) of the $CD4^+$ T cells are depleted in the gut associated lymphoid tissue and are never restored even with anti-retroviral therapy (Bharaj and Chahar, 2015; Lackner et al., 2012). Future advances in bioengineering technologies may potentially enable the

development of a therapeutic agent HIV line 5 for eliciting production of cytokines IL-17 and IFN-γ which are traditionally produced by Th17 cells thus contributing to the maintenance of the gut surface integrity and possible reducing microbial translocation, chronic immune activation and delaying or eliminating disease progression to AIDS.

Early administration of the therapeutic agents HIV lines would probably play an important role in preventing the HIV evolving rapidly brought about by the pace of replication, duration of infection and the size of the replicating population in response to host related selective influences (Coffin and Swanstrom, 2013). This would possibly result in the HIV having a lower fitness of which the replicative fitness of the founder virus is given a role in HIV immunopathology (Claiborne et al., 2015), thus possibly contributing partly to the eradication of HIV from the human host. The early administration of the therapeutic agent HIV lines would also probably induce immune responses to clear the infection before a latent reservoir is established.

A GLANCE AT THE FUTURE PROSPECTS OF BIOENGINEERED ANTI-EBOLA VIRUS AGENT

Sequencing of the Ebola virus (EBOV) which is a lethal human pathogen causing Ebola virus disease with a genome 19 kb in length and having an average case fatality rate of 78% (Dowall et al., 2014; Gire et al., 2014) revealed mutations within the genetic makeup (negative sense single stranded RNA) comprising the nucleoprotein NP, virion protein VP35, VP40, surface glycoprotein GP, VP30, VP24 and RNA-dependant RNA L Polymerase which were suggested to contribute to increased virulence of Ebola virus (Dowall et al., 2014).

The concept of 'antigenic subversion' by the surface glycoprotein GP through production of a truncated glycoprotein sGP that binds and competes for anti-GP antibodies (Mohan et al., 2012; Lai et al., 2014) makes it critical to develop a robust antibody response against GP to enable protection against lethal EBOV challenge.

Potential development of Anti-EBOV line 1 (designed GP sequences)

Future advances in bioengineering technologies including synthetic biology, nanotechnology, nanobiotechnology, genetic engineering, OMICs technologies have potential to bring to confluence bioengineering and known pathogenesis of EBOV to develop an antimicrobial therapeutic agent EBOV line 1 that has synthetic biology designed GP sequences that do not result in sGP glycoproteins. Currently trial success was exhibited with the VSV-ZEBOV recombinant, live attenuated, replication-competent genetically engineered vesicular stomatitis virus vaccine (Regules et al., 2015; Henao-Restrepo et al., 2017). The vaccine candidate (rVSV-ZEBOV) is genetically engineered to replace the VSV glycoprotein with the glycoprotein from a Zaire strain of Ebola virus (ZEBOV) (Regules et al., 2015).

Potential development of Anti-EBOV line 2 (EBOV neutralizing proteins)

Future advances of the bioengineering technologies can build on rVSV-ZEBOV to enable precision in bioengineering the antimicrobial therapeutic agent EBOV line 2 to produce fusion proteins that neutralizes the EBOV. Future advances in tagging molecular particles can enable the therapeutic agents to be specifically given 'addresses' (targeted delivery system) where the EBOV pathogen can be found in the human host.

A GLANCE AT THE FUTURE PROSPECTS OF BIOENGINEERED ANTI-*Mycobacterium tuberculosis* AGENT

Tuberculosis, an ancient disease has afflicted human beings for about 70 000 years and remains one of the major causes of human death (Cambier et al., 2014). *M. tuberculosis* exemplifies how a series of genetic adaptations can convert a soil dwelling microbe into one of the most successful pathogens of humanity (Cambier et al., 2014). *M. tuberculosis* has co-evolved with the human host to evade and exploit host macrophages and other immune cells in multiple ways (Cambier et al., 2014).

M. tuberculosis, the pathogen that causes tuberculosis has a mannose-capped lipoarabinomannan (ManLAM) on its cell envelope which is key in the bacilli ability to manipulate phagocyte functions in the lung by hijacking signaling pathways resulting in inhibition of pro-inflammatory cytokines production, inhibition of phagosome maturation, inhibition of macrophage apoptosis and inhibition of autophagy (Vergne et al., 2014). Future advances in bioengineering technologies may potentially enable the design of a therapeutic agent *M. tuberculosis* line 1 with an altered ManLAM that cannot bind to several receptors of the innate immune system which include the C-type lectins Mannose Receptor DC – SIGN and Dectin-2 (Vergne et al., 2014), as well as TR2 but at the same time is bioengineered to produce proteins that bind the ManLAM of the *Mycobacterium tuberculosis* at a higher efficiency than the receptors of the innate immune system.

A GLANCE AT OTHER POTENTIAL APPLICATIONS OF THE BIOENGINEERED THERAPEUTIC ORGANISMS

Earth's habitats have provided selection pressures over

evolutionary time that have shaped the life-forms that occur in habitats – more like a hand and glove scenario (Madsen, 2008). Human beings are not only living in habitats, but also provide habitats for microbial residents. Humans are born 100% human, but live and die 90% microbial (Madsen, 2008). Thus, over evolutionary time the human anatomy habitats have been colonized by progressively adapted microbial residents that comprise the human microbiome estimated at 10^{13} to 10^{14} microorganisms which is estimated to be ten times the number of both the human somatic and germline cells (Madsen, 2008).

The adapted microbial organisms have not all been beneficial to the human beings thus the existence of human microbial pathogens. For example, normal microbial residents and pathogens of the human skin feature specialized surface structures called 'adhesins' that facilitate cell attachment to collagen-rich interstitial areas of the skin (Madsen, 2008).

The current endeavour to decipher the human microbiome occupants in the Human Microbiome Project will potentially result in mapping the location of microbial species in the human anatomy (Cho and Blaser, 2012; Califf et al*.,* 2014; Riiser, 2015). This knowledge can potentially be used to bioengineer the beneficial human microbial residents that are mapped to sites where the pathogenesis is known to occur. This can potentially be done by employing bioengineering technologies to have a minimal genome of the identified resident microbial populations in the area of pathogenesis, and potentially adding through synthetic biology and nanobiotechnology feedback mechanisms from the whole cell based biosensor concept for detecting presence of the pathogen and thus activating production of pathogen neutralizing chemicals or proteins when the pathogen is detected.

Bioengineered human microbiome residents may potentially be used in the future to complement gene therapy of single gene disorders or human disorders that are a result of deficiency of a single protein or chemical. A first-in-man lentivirus gene therapy trial in patients with cystic fibrosis is envisaged anytime in the year 2017 (Alton et al., 2016). Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance receptor (CFTR) gene that result in impaired chloride channels. The potential use of lentivirus in gene therapy of cystic fibrosis may be complemented in the future by bioengineered human lung microbiome residents that express the correct CFTR under the control of the human cytomegalovirus enhancer/elongation factor 1α sequence, a modified EF1a promoter aiming for extended duration of expression (Alton et al., 2015). Such an approach could result in bioengineering of human microbiome residents located where the deficiency in the gene product of single gene disorders occurs. The bioengineered human microbiome resident would then provide the missing gene product potentially resulting in a successful bioengineered human microbiome resident therapeutic intervention. Future progress in bio-engineering technologies may complement gene therapy and treatment of non-communicable diseases through bioengineering of the human microbiome community.

SAFETY AND FEASIBILITY CONSIDERATIONS

The current and future rapid advancement of bioengineering technologies namely synthetic biology, bioinformatics, genetic engineering, nanotechnology, nanobiotechnology and OMICs fields has potential to augment the precision of characterizing disease pathogens and their interaction with the human host (*Homo sapiens*). This increased precision may possibly pave the way for the ability to design, build and test therapeutic agents that are targeted to critical deciphered sites where the pathogens interact with the human host and elicit production of pathogen neutralizing proteins or chemicals. The development of the therapeutic agents begs to raise concerns on safety and feasibility. To answer these concerns the therapeutic agents can be developed in several lines that are tailor made for various stages of disease progression such that the bioengineering does not require huge nucleic acid sequences to be added to the baseline minimal genomic model. On feasibility concerns, the current advancement of the bioengineering technologies has brought on the horizon synthetic biology which in the opinion of this author will increase in precision as allied technologies advance to an extent that safety considerations and feasibility studies on a designed therapeutic agent to a specific point in the human host would be achieved mostly by computer software analysis and simulations. However, development of realistic models of how the perturbation (bioengineered therapeutic agent versus pathogen) in the diseased network would affect the host organism would need to be developed to fulfill safety considerations. To this end encapsulation of the therapeutic agent with a biocompatible, semi-permeable material that allows the exchange of essential biomolecules and ions while isolating the anti-pathogen agent from the immune system of the human host (Agustín and Isalan, 2014) may become necessary.

CONCLUSION

Dr. Edward Jenner (1749-1823) who developed the vaccine against smallpox first heard a dairy maid claim: 'I can't take the smallpox, for I have already had the cowpox' (Dunn, 1996). Possibly future advances in nanobiotechnology, nanotechnology, OMICs technologies, synthetic biology and genetic engineering can result in the human species say 'I can't take the disease pathogen (HIV, *M. tuberculosis* etc), for I have the 'bioengineered antimicrobial therapeutic agent'.

CONFLICT OF INTERESTS

The author has not declared any conflict of interests.

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