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Singapore nanotechnology combats fatal brain infections

Minute Antibacterial Particles Destroy Drug-Resistant Germs

Doctors may get a new arsenal for meningitis treatment and the war on drug-resistant bacteria and fungal infections with novel peptide nanoparticles developed by scientists at the Institute of Bioengineering and Nanotechnology (IBN) of Singapore and reported in Nature Nanotechnology.

The stable bioengineered nanoparticles devised at IBN effectively seek out and destroy bacteria and fungal cells that could cause fatal infections and are highly therapeutic.

Major brain infections such as meningitis and encephalitis are a leading cause of death, hearing loss, learning disability and brain damage in patients.

IBN's peptide nanoparticles, on the other hand, contain a membrane-penetrating component that enables them to pass through the blood brain barrier to the infected areas of the brain that require treatment. The ability of IBN's peptide nanoparticles to traverse the blood brain barrier offers a superior alternative to existing treatments for brain infections. The brain membrane is impenetrable to most conventional antibiotics because the molecular structure of most drugs is too big to enter the membrane.

"Our treatment damages the structure of the pathogen and literally breaks it apart," said Yiyan Yang, Ph.D., group leader at IBN, one of the research institutes sponsored by Singapore's A*STAR (Agency for Science, Technology and Research).

"Our oligopeptide has a unique chemical structure that forms nanoparticles with membranepenetrating components on their surface," Dr. Yang added. "These nanoparticles can easily enter bacteria, yeast or fungal cells and destabilize them to cause cell death. For example, the nanoparticles cause damage to bacteria cell walls and prevent further bacterial growth."

The IBN research team has demonstrated that these engineered peptide nanoparticles have high antimicrobial activity and are highly effective in killing microbes.

Additionally, the peptide nanoparticles are more powerful in inhibiting the growth of fungal infections than conventionally available anti-fungal drugs such as fluconazole and amphotericin B.

"We are able to kill bacteria better than conventional antibiotics. By attacking the cellular structure of the microbes, our nanoparticles can be used to successfully combat persistant bacterial infections," added IBN scientist Lihong Liu, Ph.D.

Pre-clinical tests have shown that IBN's peptide nanoparticles are biocompatible and cause no damage to the liver or kidneys at tested doses. Highly anti-infective, the therapeutic doses of the peptide nanoparticles are expected to be safe for use because they also do not damage red blood cells.

IBN Executive Director Jackie Y. Ying, Ph.D., said, "Our interdisciplinary research groups have made tremendous progress in finding novel drug and gene delivery avenues for medical treatments. With this peptide nanoparticle, we have found a way through the blood brain barrier and produced a treatment for previously challenging diseases."

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The Nature Nanotechnology paper, "Self-assembled cationic peptide nanoparticles as an efficient antimicrobial agent," is authored by L. Liu, K. Xu, H.Wang, J. P. K. Tan, W. Fan, S. S. Venkatraman, L. Li and Y. Yang.

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MENIGITIS AND ENCEPHALITIS: Meningitis is an inflammation of the membranes covering the brain and spinal cord due to infection by viruses, bacteria or other microbes. Meningitis is potentially life-threatening and has a high mortality rate without treatment.

Bacterial meningitis is almost always fatal if untreated. Meningitis can cause deafness, epilepsy, brain damage, learning disabilities and other complications from fluids accumulating abnormally in the brain cavities. Encephalitis is an acute inflammation of the brain. Encephalitis is caused by a bacterial infection such as bacterial meningitis that spreads directly to the brain, or it could also be a complication of an infectious disease, e.g. syphilis and certain parasitic infections such as malaria. Meningoencephalitis is encephalitis with meningitis.

PEPTIDE NANOPARTICLES: Peptides are composed of amino acid and are the building blocks of proteins. A nanometer is approximately 5 orders smaller than the breadth of a human hair (~105 nm). On a nanoscale, IBN's antimicrobial peptide nanoparticle is a new type of nanoparticle that is self-assembled from an amphiphilic oligopeptide, which contains a component that promotes cell penetration on its surface.

BLOOD BRAIN BARRIER: The blood brain barrier refers to the brain's covering membrane, which is a layer of endothelial cells that are held together firmly by tight junctions. Substances from the bloodstream are restricted from passing through the blood brain barrier, which has a negative chemical charge. IBN's peptide nanoparticles are able to pass through this membrane into the cerebrospinal fluid and brain tissue due to the positive chemical charge on their surfaces, and the cell penetrating component on their surfaces.

MULTI-DRUG RESISTANT BACTERIA: Bacteria mutate to develop resistance to antibiotics. Bacteria that are able to withstand antibiotics and other drugs are called multi drug-resistant bacteria or "superbugs". The treatment of multi drug-resistant bacterial infections is a great challenge for medicine. IBN's peptide nanoparticles provide doctors with a novel means of treating infections that do not respond to conventional antibiotics.

Institute of Bioengineering and Nanotechnology

The Institute of Bioengineering and Nanotechnology (IBN) was established in 2003 and is spearheaded by its Executive Director, Professor Jackie Yi Ru Ying, who has been on the Massachusetts Institute of Technology's Chemical Engineering faculty since 1992, and was among the youngest to be promoted to Professor in 2001. In 2008, Professor Ying was recognized as one of "One Hundred Engineers of the Modern Era" by the American Institute of Chemical Engineers for her groundbreaking work on nanostructured systems, nanoporous materials and host matrices for quantum dots and wires. Under her direction, IBN conducts research at the cutting-edge of bioengineering and nanotechnology. Its programs are geared

towards linking multiple disciplines across all fields in engineering, science and medicine to produce research breakthroughs that will improve healthcare and our quality of life.

IBN's research activities are focused in the following areas:

- Drug and Gene Delivery, where the controlled release of therapeutics involve the use of functionalized polymers, hydrogels and biologics for targeting diseased cells and organs, and for responding to specific biological stimuli.
- Cell and Tissue Engineering, where biomimicking materials, stem cell technology, microfluidic systems and bioimaging tools are combined to develop novel approaches to regenerative medicine and artificial organs.
- Biosensors and Biodevices, which involve nanotechnology and microfabricated platforms for high-throughput biomarkers screening, automated biologics synthesis, and rapid disease diagnosis.
- Pharmaceuticals Synthesis and Nanobiotechnology, which encompasses the efficient catalytic synthesis of chiral pharmaceuticals, and new nanocomposite materials for sustainable technology and alternative energy generation.

IBN's innovative research is aimed at creating new knowledge and intellectual properties in the emerging fields of bioengineering and nanotechnology to attract top-notch researchers and business partners to Singapore. Since 2003, IBN researchers have produced a total of 490 papers published/in press, of which 223 were published in journals with impact factor greater than 3. IBN also plays an active role in technology transfer and spinning off companies, linking the research institute and industrial partners to other global institutions.

As of March 2009, IBN has filed 692 patent applications on its inventions and the Institute is currently looking for partners for collaboration and commercialization of its portfolio of technologies. IBN's current staff strength stands at around 170 scientists, engineers and doctors. With its multinational and multidisciplinary research staff, the institute is geared towards generating new biomaterials, devices, systems, equipment and processes to boost Singapore's economy in the fast-growing biomedical sector.

IBN is also committed to nurturing young minds, and the institute acts as a training ground for Ph.D. students and undergraduates. In October 2003, IBN initiated a Youth Research Program to open its doors to university students, as well as students and teachers from various secondary schools and junior colleges. It has since reached out to more than 31,000 students and teachers from 204 local and overseas schools and institutions.

For more information, please log on to www.ibn.a-star.edu.sg