NEWS RELEASE
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A*STAR SCIENTISTS DISCOVER HOW TO COMBAT HOSPITAL-ACQUIRED INFECTIONS, DEADLY FOOD POISONING AND BIOTERRORISM TOXINS

This study paves the way for developing toxin antidotes to safeguard public health and national security.

A team of scientists from A*STAR’s Institute of Molecular and Cell Biology (IMCB) has discovered the secret recipe for ‘antidotes’ that could neutralize the deadly plant toxin Ricin, widely feared for its bioterrorism potential, as well as the Pseudomonas exotoxin (PE) responsible for the tens of thousands of hospital-acquired infections in immuno-compromised patients all over the world. The results of this first ever genome-wide study to understand how the Ricin and PE toxins attack cells may also be useful for designing more effective antidotes against Diphtheria\(^1\) and Shiga-like toxins secreted by infectious strains of E. coli bacteria, such as those responsible for the recent food poisoning outbreak in Germany.

2. In this study, the team led by IMCB Principal Investigator, Dr Frédéric Bard examined the entire human genome of about 22,000 genes to identify those genes of normal host cell processes which Ricin and PE toxins hijack in order to kill the cell. Of the several host genes identified, the team discovered one called ERGIC2 to be an attractive therapeutic target because it is not only highly essential for Ricin but also required for PE intoxication. “This means that we could potentially develop a generic antidote that is effective against the two different types of toxins by blocking ERGIC2 function,” said Dr Bard.

3. Ricin is an extremely potent poison that can easily be purified from the widely available castor beans. Security experts say an amount roughly equivalent to half a grain of rice is enough to kill an adult, making it 1,000 times more poisonous than cyanide. There are currently no known antidotes for Ricin, and the ease of production of this tasteless, odorless plant toxin is why ricin is feared for its immense bioterrorism potential.

4. Hospital-acquired infections (HAIs) are a major healthcare problem affecting millions of people around the world. The U.S. Centers for Disease Control and Prevention estimates that HAIs leads to US$45 billion in healthcare cost annually and results in nearly 100,000 deaths per year, making HAIs the fourth leading cause of death. The bacteria Pseudomonas aeruginosa that secretes PE toxin is a common cause of HAIs in vulnerable individuals, including those with burn injuries or receiving

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\(^1\) Diphtheria is an infectious disease of the upper respiratory tract caused by Corynebacterium diphtheria. Diphtheria toxin can spread through the bloodstream, if untreated it may cause permanent damage to vital organs such as the heart, lungs and kidneys.
intensive care. Unfortunately, HAIs are increasingly difficult to treat because the emergence of antibiotic-resistant bacteria is on the rise. Similarly, the *E. coli* strain that produces Shiga toxins, found in the recent deadly food poisoning cases in Germany, were also resistant to antibiotics. Moreover, in food poisoning cases caused by such toxin-producing bacteria, doctors refrain from using antibiotics as killing the bacteria actually causes more toxins to be released, bringing on the worst symptoms of the illness\(^2\). There is therefore a real need worldwide for antidotes against these life-endangering toxins.

5. Highlighting the significance of this study, Dr Bard added, “Through this genome-wide screen, our understanding of how toxins interact with human cells at the molecular level expanded tremendously. Our hope is that with these new therapeutic targets identified from the human genome, we will be one step closer to finding toxin antidotes that will make hospital-acquired infections and enterotoxic *E. Coli* outbreaks a thing of the past.”

**More about protein toxins**

6. Though immunologically different from each other, Ricin, PE, Diphtheria and Shiga toxins all kill by destroying the cell’s protein synthesis ‘factories’, the place where all proteins necessary for the cell’s survival are produced. To travel to these protein ‘factories’ in the cell, the toxins first trick the host cell into turning off a natural defense mechanism that destroys foreign proteins. Next, they exploit the host cell’s internal transport pathway to reach the protein ‘factories’, destroying them and killing the cell. When this happens, cell death is imminent. If not contained, toxins released from dead cells can spread to neighboring healthy cells, resulting in rapid and widespread tissue and organ damage.

7. By identifying the specific host genes required for these toxins to attack the cell’s protein ‘factories’, this study effectively singled out the attractive therapeutic targets from the entire human genome for developing antidotes that could potentially be effective against any toxins that share the same mode of action. For instance, ERGIC2 was found to be an important component of the cell’s internal transport pathway that the toxins hijack to reach the cell’s protein ‘factories’.

**Notes for Editor:**
The research findings described in this news release can be found in the 21 July 2011 advance online issue of *Developmental Cell* under the title, "**Genome-wide RNAi screens identify genes required for Ricin and PE intoxications**" by Dimitri Moreau, Pankaj Kumar, Shyi Chyi Wang, Alexandre Chaumet, Shin Yi Chew, Hélène Chevalley and Frédéric Bard.

\(^2\) Shiga-like toxins specifically attack the membrane lining of intestines, lungs and kidneys, triggering a massive wave of dying cells. Food poisoning with Shiga-like toxins often leads to widespread haemorrhage which may cause extensive and permanent organ failure, and sometimes even death.
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About Institute of Molecular and Cell Biology (IMCB)

The Institute of Molecular and Cell Biology (IMCB) is a member of Singapore's Agency for Science, Technology and Research (A*STAR) and is funded through A*STAR’s Biomedical Research Council (BMRC). It is a world-class research institute that focuses its activities on six major fields: Cell Biology, Developmental Biology, Genomics, Structural Biology, Infectious Diseases, Cancer Biology and Translational Research, with core strengths in cell cycling, cell signalling, cell death, cell motility and protein trafficking. Its achievements include leading an international consortium that successfully sequenced the entire pufferfish (fugu) genome. The IMCB was awarded the Nikkei Prize 2000 for Technological Innovation in recognition of its growth into a leading international research centre and its collaboration with industry and research institutes worldwide. Established in 1987, the Institute currently has 26 independent research groups, eight core facilities and 300 researchers.

For more information about IMCB, please visit www.imcb.a-star.edu.sg

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