BIODEFENCE
NEST ADVENTURE

Antibody fragment producing lactobacilli binding to beads covered with the appropriate antigen – an adhesin from Streptococcus mutans.

Countering bioterrorism with passive immunisation

In the event of a bioterrorist attack, exposed populations would be completely unprotected because there are no products available for rapid vaccination. The BIODEFENCE project aims to engineer bacteria 'generally regarded as safe' to produce toxin-neutralising antibodies in the intestinal mucosa. Administered via food or drinking water, the bacteria should confer quick protection. Although developed to counter weapons of bioterrorism (anthrax and botulism), the approach could be applied much more widely.

The recent anthrax scare in the USA has enhanced public concern about bioterrorism, highlighting the absence of quick, effective ways to protect exposed populations. Antibiotics act only against sensitive bacteria (as opposed to viruses or bacterial toxins), and for many pathogens there exists no safe, effective vaccine licensed for public use. When a vaccine is available, multiple doses are required to build up, over months, a sufficient level of immunity. Selected at-risk groups (e.g. soldiers) can be vaccinated preventively, but conventional vaccination is inadequate for quick protection of large populations in an emergency.

Conventional vaccines rely on 'active' immunisation, i.e. the use of an antigen to stimulate antibody production by the vaccinated subject. Another approach, sometimes used in emergency situations, is 'passive' immunisation: administration of ready-made antibodies. But this is a costly solution, requiring mass production and purification of antibodies under strict quality control, and the treatment must continue as long as high antibody levels are to be maintained.

BIODEFENCE is a three-year project based on an idea that may revolutionise passive immunisation: engineering bacteria 'generally regarded as safe' (GRAS) to produce toxin-neutralising antibodies at the site where they are needed. The project focuses on bacteria that naturally colonise the human intestinal mucosa and on the toxins of two mucosal pathogens: the agents of anthrax and botulism. The protective GRAS bacteria could be mass-produced at low cost and added to food or drinking water. Hopefully they would persist in the mucosa and confer protection over an extended period.

Proof of concept

The expertise of the five BIODEFENCE partners (based in Sweden, Estonia, Spain, the Netherlands, and the USA) spans a wide range of life-science disciplines and molecular techniques. A prime objective will be to achieve proof of concept. This will be done with a laboratory strain of lactobacillus, genetically modified to produce antibodies targeting the botulism toxins or a component of the anthrax toxin (a plasmid-based expression system is

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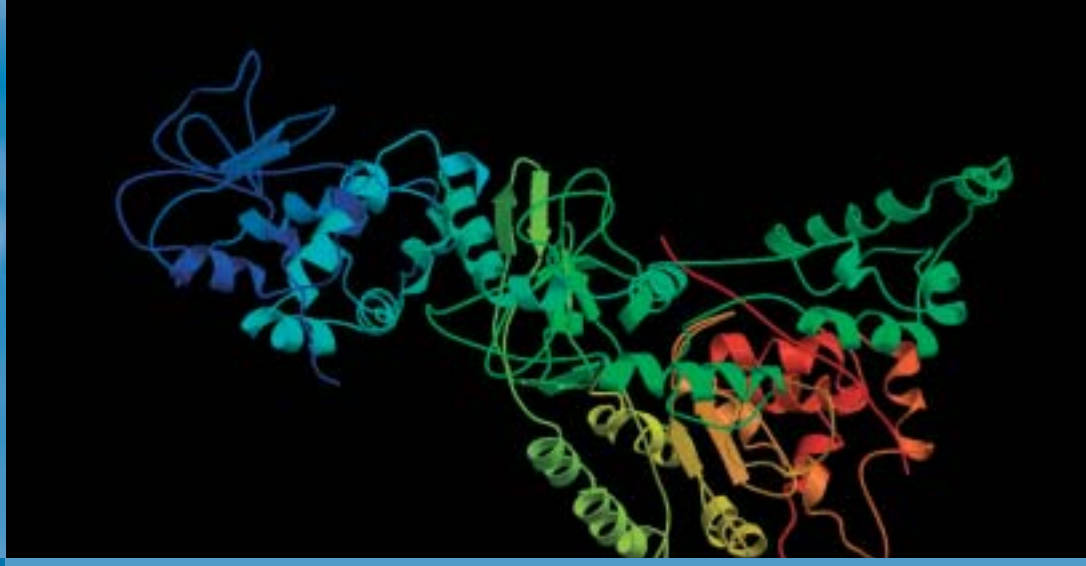

The recent anthrax scare has enhanced public concern about bioterrorism.
Crystal structure of the anthrax lethal factor. © Informations Sekretariat Biotechnologie

BIODEFENCE
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AT A GLANCE

Official title
Rapid induction of passive immunity against weapons of bioterrorism using transformed GRAS (generally regarded as safe) micro-organisms

Coordinator
Sweden: Karolinska Institutet

Partners
- *Estonia: University of Tartu*
- *Spain: Consejo Superior de Investigaciones Cientificas*
- *The Netherlands: Lactrys Biopharmaceuticals BV*
- *USA: University of Alabama*

Further information
Prof Lennart Hammarström
Karolinska Institutet, Division of Clinical Immunology, Department of Laboratory Medicine, Huddinge University Hospital, Stockholm, Sweden
Fax: +46 (0)8 585 813 90
E-mail: lennart.hammarstrom@biosci.ki.se

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already available). An animal model will be used to test the ability of these modified bacteria to confer protection against anthrax or botulism.

In parallel, partners will develop and optimise the approach for use in humans. One task is to select strains of human gastrointestinal lactobacilli that persist in the human digestive tract, are suitable for genetic manipulation, and readily colonise the intestinal mucosa (to be demonstrated on human volunteers). Another important task is to develop a food-grade gene expression system offering all necessary safety guarantees. This notably means ensuring that marker genes conferring antibiotic resistance are eliminated from the expression constructs and that the antibody genes remain confined within the GRAS bacteria. Once this work is done, an animal model will be used to test expression of the antibody-encoding genes, expression-construct stability, and protection.

Beyond bioterrorism

If this project is successful, its societal impact could be great. Antibody-producing mucosa-colonising bacteria might be used against a wide variety of diseases, within or beyond the context of bioterrorism. A good target, for instance, might be rotavirus, which kills nearly a million people (mostly children in developing countries) each year. Administered anti-rotavirus antibodies, on the one hand, and selected lactobacillus strains, on the other, are known to confer some protection. Might antibody-producing lactobacilli work even better?

Antibody-producing, mucosa-colonising bacteria might be used against a wide variety of diseases, either within or beyond the context of bioterrorism.

This innovative approach might extend to pathogens affecting the mucosae of the lungs, mouth, or stomach. If suitable vagina-colonising GRAS bacteria are isolated, it might also apply to sexually transmitted diseases (even HIV). In both developed and developing countries, it could provide a cost-effective way to address major public health problems on a large scale.

SIXTH FRAMEWORK PROGRAMME