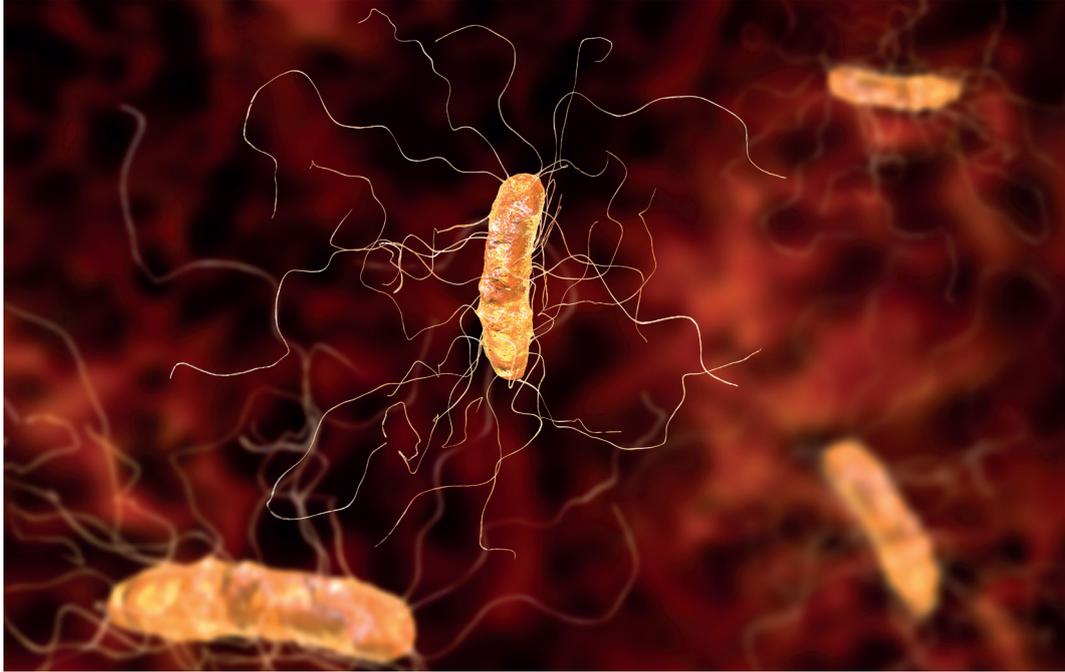


SEARCH FOR NATURAL SOLUTIONS FOR CONTROLLING PATHOGENIC CLOSTRIDIA



TNO innovation
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TNO is searching for partners for a consortium research project aiming at the identification of novel solutions for controlling pathogenic Clostridia such as *Clostridium difficile* and *C. perfringens*. These are a serious threat for human and animal health and a major reason for using antibiotics. Novel solutions preventing disease development will lead to a reduction in antimicrobial resistance development and fit with global One Health goals.

Pathogenic Clostridia include *C. tetani* (CT), *C. botulinum* (CB), *C. difficile* (CD) and *C. perfringens* (CP). The incidence of life threatening disease caused by CT and CB nowadays is very low in the Western world, but for CD and CP the situation is quite different. With hundreds of thousands cases of CD infections yearly, this infection has become a major infectious disease in humans leading to multibillion euros healthcare costs. At the same time CP is a major infectious disease in poultry and pigs.

The biology of these pathogenic *Clostridia* shows some striking resemblances. They are all strictly anaerobic organisms only growing in environments without oxygen, and can cause disease by the toxins they produce. These toxins are among the most toxic compounds on earth. Due to their ability to produce spores they are highly resistant to

environmental stressors (including oxygen and antibiotics, but also heat and disinfectants) which allows for spreading these organisms. This resistance is also a major reason for their increased incidence.

Current strategies mainly aim at treating infection caused by pathogenic *Clostridia*. Antibiotic treatment is the most common treatment, although its side effects are getting more attention. Other treatments include antibodies targeting toxins and more drastic approaches such as fecal transplants.

Here we aim for a different approach, namely prevention of these life threatening infections instead of treating them. By combining novel technological platforms and specific insight in the biology of these bacteria we feel novel solutions should be within reach.

TNO will bring in its long term expertise in gut microbiota and health, including anaerobic microbiology, bacterial spores, intestinal microbiota and host microbe biology and screening technology. This includes the i-screen platform in which the *in vivo* microbiota composition can be mimicked in a medium throughput *in vitro* set up. Organisms such as CD and CP can be maintained in an i-screen system allowing for screening conditions much closer to the *in vivo* situation than in standard pure culture screening. Also the InTESTine platform which is based on intestinal epithelium obtained for human or pig and allows for medium throughput experiments looking into the interaction between toxins or toxigenic bacteria with the intestinal tissue will be part of the proposed project

A major challenge for this project will be the identification of solutions specifically targeting pathogenic Clostridia without harming the commensal or even beneficial Clostridia which are also present in the GI-tract. Some of these Clostridia have been shown to play an important role in driving the intestinal immune system into an anti-inflammatory response, an effect strongly linked to the healthy state.

Potential solutions for combatting pathogenic Clostridia can be based on the following mechanisms:

- inhibition of spore germination
- competitive exclusion of the CD/CP by supporting a stable gut microbiota
- supporting epithelial adherence of beneficial microbes by prebiotics and/or probiotics
- introduction of competitive probiotics
- in situ production of anti-CD/CP activity by probiotic lactobacilli (bacteriocin producing)
- inhibitory effects of specific metabolites
- interference with toxin production or toxin activity

Potential partners may be:

- medical/clinical food companies
- food supplement/probiotic/prebiotic companies
- pharmaceutical companies

The project structure will be as follows:

- Public Private Partnership
- Partly funded by the Dutch government through TKI-LSH
- Annual contribution by industrial partners
- Annual Go-No Go per partner
- Intended duration: 3 years

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TNO HEALTHY LIVING

TNO connects people and knowledge to create innovations that boost the sustainable competitive strength of industry and well-being of society. This is our mission and it is what drives us, the 2,600 professionals at TNO, in our work every day.

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