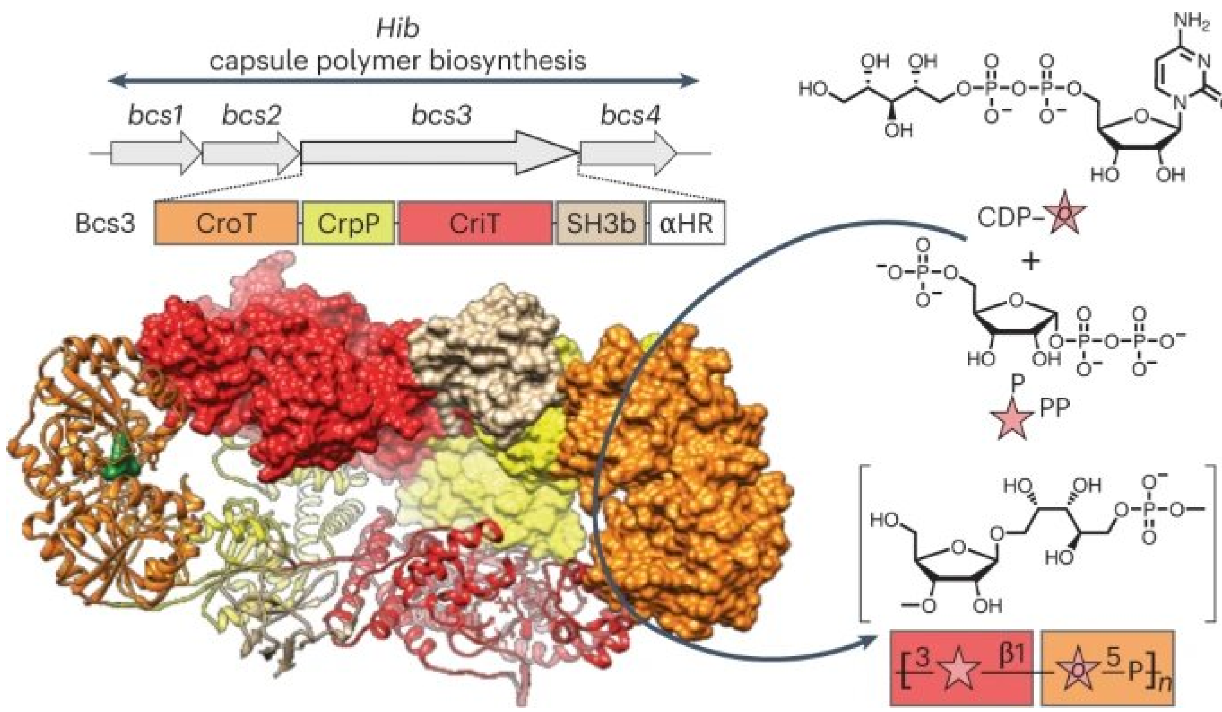
Study discovers potential key to a cheaper and more accessible Haemophilus influenzae type b vaccine

June 6 2023



Credit: *Nature Chemical Biology* (2023). DOI: 10.1038/s41589-023-01324-3

The bacterium Haemophilus influenzae type b (Hib) can cause severe diseases such as meningitis and blood poisoning in young children. Researchers from the MHH Institute of Clinical Biochemistry have deciphered the pathway of the bacterial capsule and created the basis for producing an Hib vaccine that is inexpensive and safe.

The bacterium Haemophilus influenzae type b (Hib) inhabits the human nasal cavity. It causes infections of the upper and lower respiratory tract, especially in infants and young children. But even more serious diseases such as middle ear inflammation, meningitis or blood poisoning (sepsis) can be caused by Hib. The bacterium surrounds itself with a shell consisting of many sugar chains, which are also referred to as capsule polymers. With the capsule polymers, the bacterium protects itself against the host's immune system and can thus survive in the human body.

Vaccines against Hib are available that contain the sugar polymers in the capsule and train the immune system to these antigens. However, their production is complex and expensive. This is because the antigens must be obtained directly from infectious bacterial cultures, which requires a laboratory with an adequate level of safety.

The team led by Dr. Timm Fiebig from the Institute of Clinical Biochemistry at the Hannover Medical School (MHH) has now succeeded in fully deciphering the path of formation of the capsule polymer for the first time, thus creating the potential to produce the vaccine antigen cheaply and safely by enzymatic synthesis without the use of pathogens. Their results have been published in the journal *Nature Chemical Biology*.

Simple synthesis could make vaccine more accessible worldwide

"The elucidation of the biosynthesis pathway enables a much more elegant production of Hib vaccine antigens from widely available and inexpensive precursors in a standard laboratory, without having to grow dangerous bacteria in bioreactors," says Dr. Fiebig, head of the working group Microbial Glycobiochemistry and Vaccine Development.

Despite the high effectiveness of the Hib vaccine introduced in Germany in the 1990s, the bacterium is still the main cause of bacterial meningitis in children under 1 year of age in unvaccinated societies. Thanks to the simplicity of the newly discovered synthetic pathway, the distribution of the vaccine could be improved worldwide.

Possible approach for new vaccines and drugs against bacteria

However, the research team has not only elucidated the production path itself, but also described the enzymes that control this process. "We have now for the first time comprehensively understood how the bacterium builds its polymer capsule and which enzymes it uses as tools for this," says Dr. Fiebig. This enzyme factory can now be reproduced in the test tube under safe conditions. The most important enzyme is the so-called capsule polymerase, which produces the actual polysaccharide capsule and thus the antigen for the vaccine.

The enzyme consists of four subunits. Three of them transfer chemical building blocks that occur in the surface polymers of many other bacteria and contribute to the pathogenic effect of the pathogens. However, it was not yet known which enzymes transmit these building blocks and what these enzymes look like three-dimensional. However, this is crucial for the development of antibacterial agents and for the discovery of new enzymes that control how bacteria cheat our immune system and how infectious they are.

The researchers were also able to identify the same polymerase structures in other bacteria. These include the intestinal bacterium

Escherichia coli, the most antibiotic-resistant Acinetobacter species, or even the listeria found on contaminated foods.

"Our findings could also be used to develop vaccines or drugs against these and other pathogens, for example by developing substances that block the newly discovered enzymes and thus interrupt the formation of the protective capsule," says Dr. Fiebig. In view of the increasing resistance to antibiotics, this is a promising option in the fight against bacteria. However, further research is needed to achieve this.

More information: Javier O. Cifuente et al, A multi-enzyme machine polymerizes the Haemophilus influenzae type b capsule, *Nature Chemical Biology* (2023). DOI: 10.1038/s41589-023-01324-3

Provided by Medizinische Hochschule Hannover

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