Conjugation chemistry creates affordable childhood vaccines

The immune system provides a formidable defence against pathogens. However, many bacteria possess a protective sugar polymer coat. In children, the immune system does not respond to these polymers unless they are chemically linked to a carrier. This is the basis of conjugate vaccines, a powerful but expensive means to fight diseases like pneumonia, the leading cause of death in the under-fives. Andrew Lees, CEO of Fina Biosolutions and adjunct professor at the University of Maryland, USA, has developed a simple yet efficient approach to synthesize conjugate vaccines. Together with a ‘not-for-much-profit’ model, his innovative technology is accelerating the impact of vaccines, particularly in developing countries.

The body’s resistance to pathogens relies on the immune system: a sophisticated and incredibly complex network of biological processes. It coordinates the fight against viruses, bacteria, parasitic worms, cancer cells, and even foreign objects like wood splinters. The immune system employs an army of antibodies, a large group of Y-shaped proteins that can bind to foreign invaders, marking them for destruction.

**ADAPTIVE RESPONSE**

An important component of our ‘adaptive’ immune system, antibodies are very specialised, attacking only their specific targets. Over the course of our lives, this adaptive response learns how to recognise dangerous pathogens and how to trigger the biochemical response to kill and eliminate them from our bodies. Human-made vaccines exploit this ability of the immune system to learn from previous fights: they contain an agent that resembles a weakened pathogen, in the form, for instance, of killed microbes, their inactivated toxins, or some of their surface proteins. These agents ‘teach’ the body how to respond to the threats posed by the natural pathogen. As the protective component has become better defined, more purified components (antigens) are used for vaccines. However, some antigens will not induce an antibody response unless they are chemically linked (conjugated) to a protein, which serves as the ‘carrier’. Immunisation with the conjugate vaccine will cause the body to make antibodies to the antigen.

**VACCINE RESISTANCE**

Several bacteria that cause invasive diseases have evolved the ability to protect themselves from a host’s immune system by shredding their cell membranes with a protective layer of polysaccharides. These molecules, known as capsular polysaccharides, are composed of long chains of carbohydrates (sugar) repeat units, forming layers of polyp disperse polymers covering the surface of the bacteria. They are found, for instance, on pneumococcal bacteria (also known as Streptococcus pneumoniae), which are responsible for community-acquired pneumonia and meningitis in children and the elderly.

More than 90 different varieties of pneumococci are known, each exhibiting a chemically distinct capsular polysaccharide. The capsule-specific antibodies can help protect humans against diseases caused by pneumococci. However, the ability of the body to produce these antibodies matures only with age. For this reason, unlike adults, children can be very vulnerable to bacterial diseases caused by encapsulated pathogens, like pneumococci.

**CONJUGATE VACCINES**

More than 70 years ago, it was found that purified high-molecular-mass polysaccharides from pneumococci induce specific antibodies in adults, promoting resistance to the diseases caused by this class of bacteria. In children, however, this approach failed to elicit an immune response. It was later found that by conjugating the polysaccharides with a protein carrier, the conjugate would now induce an antibody response to the polysaccharide in children.

The first approved and marketed example of this conjugation chemistry was a vaccine against Haemophilus influenzae b (Hib), a bacterium responsible for childhood meningitis, pneumonia, and epiglottitis, which, before the introduction of the vaccine in the 1980s, was estimated to be responsible for 20,000 cases in the USA alone. The vaccine reduced the incidence of the disease by more than 99%.

**CDAP: A BREAKTHROUGH IN CONJUGATION CHEMISTRY**

Conjugate vaccines have been developed to fight some of the most devastating paediatric diseases worldwide, including, in addition to Hib, those caused by Streptococcus pneumoniae, Salmonella typhi, and Neisseria meningitidis. Creating conjugate vaccines, however, requires complex multi-step chemical processes. This makes them some of the most expensive and complicated vaccines in existence. The high cost of conjugate vaccines can limit their use, especially in those cases where they would be most required, like mass vaccinations of young children in developing countries.

Andrew Lees, CEO of Fina Biosolutions and adjunct professor at the University of Maryland, USA, has developed an innovative approach that simplifies the complex chemistry of polysaccharide-protein conjugation. The crux of his approach is a chemical reaction called CDAP (Cyclic Diammonium Phosphate), a simple yet efficient method to synthesise conjugate vaccines.
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CONJUGATE VACCINES FOR DEVELOPING COUNTRIES
The bioengineered E. coli approach developed by Fina Biosolutions for the production of CRM197 has also been licensed to PATH, a US-based global-health non-profit organisation, for meningococcal disease. The conjugate vaccine for pneumonia and meningococcal disease is estimated to have saved tens of thousands of lives.

CONJUGATE VACCINES
For vaccine development. He holds 25 patents in the field of conjugate vaccines. The realisation of CDAP chemistry was a true scientific ‘eureka’ moment. One night, alone in the lab, I activated a polysaccharide with CDAP and added the protein, instantly forming a gel. I told my wife that I thought I had done something important. Although it took many more months to develop the chemistry where it was useful for conjugate vaccines and many years of effort to prove its value, that moment in the lab changed my life by giving me work a focus and purpose. I am proud to know that the chemistry I developed is used in vaccines that have saved tens of thousands of lives.

REFERENCES
- Lees, A., Bart, JF, Galoestrae, S. (2020) Activation of soluble polysaccharides with 1-cyano-4-dimethylamino-pyridine tetrafluoroborate (CDAP) for use in protein-polysaccharide conjugate vaccines and immunological reagents. II. Optimisation of CDAP activation. Vaccine, 8:777. doi.org/10.13090/vaccine80777