Synthetic virus developed to deliver a new generation of medicines

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Paul van der Schoot. Credit: Bart van Overbeeke.

Researchers at the universities of Wageningen, Eindhoven, Leiden and Nijmegen have developed a synthetic virus. This can be used in the future to 'package' new generations of medicines consisting of large biomolecules and to deliver them into diseased cells, by a natural process. Prof.dr.ir. Paul van der Schoot at TU/e was responsible for the basic theoretical research. The results also confirm that he has solved a thirty-year-old question. The work was published last Sunday in *Nature Nanotechnology*.

New types of medicines consist of large biomolecules such as DNA and RNA. Delivering these to diseased cells is challenging. For example DNA is inherently unable to penetrate inside cells, and is quickly broken down. This is why natural viruses which have been made harmless are used to deliver these medicines. Viruses can efficiently penetrate into cells, but the process of making natural viruses harmless has not yet been perfected. Scientists are therefore searching for alternatives.

Thirty years

The research published in *Nature Nanotechnology* is based on a theoretical model that describes how the tobacco mosaic virus is produced. Paul van der Schoot (Applied Physics department) recently developed this model together with dr. Daniela Kraft of Leiden University. Van der Schoot used measurement data from the formation of this virus, which had remained unexplained for the last thirty years.

Enzyme attack

A virus always consists of genetic material (DNA or RNA), encapsulated in a coat of protein. These enable viruses to enter the cells. Missing parts of the genetic material are fatal for this process because they allow enzymes to attack the material. In his model Van der Schoot added vital missing link to the existing understanding of how the RNA of the tobacco mosaic virus collects a surrounding protein coat.

Proof

This missing link is called allosteric regulation, and enables proteins to help each other to bond to the RNA. "It's difficult for the first protein to bond", explains Van der Schoot. "But the first helps the second, and the second helps the third, and so on." He used this theoretical understanding

together with Renko de Vries of Wageningen UR to write a research proposal for the packaging of a DNA-like molecule. This allowed them to develop new 'packaging proteins' bases on the theory. The fact that this produced the desired result is important for medicines to correct genetic defects, for example. It also proves Van der Schoot's theoretical model. TU/e PhD candidate Saber Naderi gained his doctorate earlier this year on this research.

Nanometers

There's also another Eindhoven aspect to this story: TU/e researcher Nico Sommerdijk was able to clarify the packaging process. This takes place on a nanometer scale, so it requires the use of the university's cryoTEM microscope.

Yeast cells

The proteins built by the researchers are inspired by natural proteins such as those found in silk and collagen; protein segments with a simple structure. To 'produce' these proteins they used the natural machinery of yeast cells. When the synthetic virus proteins are mixed with DNA they are spontaneously covered with a strong protective protein coat around each DNA molecule, producing 'synthetic viruses'.

The researchers expect that the high degree of precision with which the proteins 'package' the DNA molecules offers numerous opportunities to incorporate other features of viruses. These may in the future lead to safe and effective ways to deliver new-generation medicines, especially in gene therapy. In addition, the synthetic viruses may in the future be further developed for the many other applications for which viruses are already used in bio- and nanotechnology.