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Key hurdle overcome in the development of a drug against cystic fibrosis

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Researchers from Eindhoven University of Technology and McGill University in Montreal (Canada) have taken an important step towards developing a drug against cystic fibrosis. In people suffering from this illness the CFTR protein is not located in the right place in mucus-producing cells: it remains inside the cell while it should be in the cell wall. Those cells secrete a tough mucus with serious consequences. However, the researchers have succeeded in conducting the CFTR to the cell walls. Their findings are published this week in the leading science journal *PNAS*.

The human body produces mucus, which fulfills key functions in all kinds of places. For instance, mucus helps to remove substances and bacteria you breathe in. Mucus also transports digestive agents or enzymes from the pancreas to the small intestine. If the mucus is tough, it is less able to remove waste substances. The mucus will also tend to accumulate in different organs, with disastrous consequences. The life expectancy of someone suffering from cystic fibrosis is around 40 years.

The researchers managed to isolate a fundamental characteristic of the illness in a laboratory. In around seventy percent of the Caucasian population with the illness, the cause was found to be that the protein 'cystic fibrosis transmembrane conductance regulator' (CFTR) contains anomalies, and so remains inside the cell wall. It was already known that a different kind of protein, called 14-3-3, which is naturally present in the cells of healthy individuals, plays a role in transporting the CFTR to the cell wall. The scientists have now found a naturally occurring

substance, fusicoccin-A, which can nonetheless ensure that this transport does take place.

Whether a drug can be developed to halt cystic fibrosis still remains to be seen. First of all, the researchers have to see whether the mutant CFTR, which is contained in the cell wall, helps produce liquid mucus and how much. Then they will have to find an alternative to fusicoccin-A, with the same healing effect and optimum drug properties, since fusicoccin-A has a number of properties that do not predispose it to being a suitable drug: the solubility, for example, is not ideal and production costs are high.

Different companies have already shown interest in the results.

More information: Loes M. Stevers et al. Characterization and small-molecule stabilization of the multisite tandem binding between 14-3-3 and the R domain of CFTR, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1516631113

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