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Cystic fibrosis: New compounds display strong therapeutic potential

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Cystic fibrosis is a lethal genetic disorder that in France affects one child per 4,500 births. An international team led by scientists at the Institut Fédératif de Recherche Necker-Enfants Malades (CNRS/Inserm/Université Paris Descartes), led by Aleksander Edelman, has recently discovered two new compounds that could be used to treat patients carrying the most common mutation. By means of virtual screening and experiments on mice and human cells in culture, the scientists were able to screen 200,000 compounds and selected two that allowed the causal mutated protein to express itself and fulfill its function.

These findings were recently published online in *EMBO Molecular Medicine*.

Cystic fibrosis is a genetic disorder that affects the epithelia of numerous organs, and particularly those in the lungs, pancreas and intestine. In the lungs, this takes the form of insufficient epithelial hydration, resulting in excess mucus in the bronchi. This mucus retains pathogenic agents and favors the onset of chronic infections and inflammatory conditions that are ultimately fatal to the sufferer.

The disease is caused by mutations in the gene coding for a protein called CFTR (cystic fibrosis transmembrane conductance regulator). This protein, which is essential to ensure the passage of water through an epithelium, is an ion channel that allows chloride ions to pass through cell membranes. To date, about 2,000 gene mutations that cause the

disease have been determined, but 70% of cases of cystic fibrosis are due to a single mutation called ?F508. And it is this mutation that is targeted by the recently-discovered compounds.

The scientists used computer techniques to screen 200,000 compounds, looking for those that might interact with a specific zone in the abnormal protein, and found about a dozen potentially active molecules. Using these 12 compounds, they then performed in-vitro tests on human cell cultures and in-vivo experiments on mice showing this mutation. They were thus able to observe that two of these compounds allowed the mutated delta-F508-CFTR protein to be trafficked to the membrane and fulfill its role.

One of the highlights of this work was that the scientists were able to describe the mechanism of action of these two compounds. In itself, and despite its mutation, the delta-F508-CFTR protein may satisfactorily fulfill its function. The problem is that once it is synthesized, it is recognized as being abnormal by keratin 8, another protein which favors its degradation, thus preventing delta-F508-CFTR from reaching the cell membrane. The compounds discovered by the scientists inhibit the interaction between keratin 8 and delta-F508-CFTR so that the protein can be deployed appropriately and fulfill its role as an ion channel. The scientists think that for potential therapeutic purposes, the two molecules they have discovered could be associated with "potentiating" compounds that would enhance the activity of delta-F508-CFTR.

The scientists now want to determine whether these two compounds do indeed cause a reduction in the susceptibility to infection of cystic fibrosis mice models. They also hope to start clinical trials in cystic fibrosis patients in the coming years.

More information: Discovery of novel potent delta-F508-CFTR correctors that target the nucleotide binding domain, Norbert Odolczyk,

Janine Fritsch, Caroline Norez, Nathalie Servel, Melanie Faria da Cunha, Sara Bitam, Anna Kupniewska, Ludovic Wiszniewski, Julien Colas, Krzysztof Tarnowski, Danielle Tondelier, Ariel Roldan, Emilie L. Saussereau, Patricia Melin-Heschel, Grzegorz Wieczorek1, Gergely Lukacs, Michal Dadlez, Grazyna Faure, Harald Herrmann, Mario Ollero, Frédéric Becq, Piotr Zielenkiewicz, Aleksander Edelman, EMBO : DOI: 10.1002/emmm.201302699