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ΔF508-CFTR correctors deriving from computational design and from safe natural compounds for a prompt clinical application

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Background. Our research is designed to increase the number of useful substances for treating CF patients with ΔF508 mutation. In particular, our efforts are aimed at expanding the sector of "correctors."

Hypothesis and objectives.
1) Finding, through rational systems, molecules interacting with the mutant CFTR or those proteins responsible for its degradation in order to rescue the ΔF508-CFTR.
2) Discovering new potential correctors between natural substances already present in foodstuff or herbal medicines. Such substances could reach the market in less time than the synthetic drugs.

Methods.
1) Through the molecular design (MD) assisted by computer, we have selected a set of substances able to bind to specific sites on proteins involved in CF and provided of known crystallographic data. The time machine was purchased by Google. The structures for "virtual screening" were taken from the Zinc Database containing more than 5 millions of "drug-like" molecules, all present in the market.
2) Based on a structural motif found in some well-known correctors, ca. 30 phenylhydrazones were synthesized. These substances have been tested on cells CFBE410- evaluating the iodide influx by the quenching of fluorescence.
3) Natural products have been tested on FRT cells (influx of iodide) and A549 cells (western blot).

Results.
1) About 1,000 molecules were selected using the MD. Now such molecules are going to further reductions of that amount using the docking flexibility to obtain more significant and manageable data. So far there are no experimental data on cells.
2) Two phenylhydrazones (namely, SM5 and SM20) showed an interesting activity as correctors when tested at 20 mM and 2 mM, respectively.
3) Within the framework of investigations on natural products, our data show that citric acid and tartaric acid (tested at 10 μM) have a moderate correction activity on A549 cells.
4) An excellent result came from further research on the alkaloid Matrine. When VX-809 (corrector) and VX-770 (potentiator) were added to FRT cells 24 h after the introduction of Matrine (actually, Matrine must take the time to fulfil its role as downregulating the chaperone HSC70), a significant increase of the influx of iodide was appreciated.

Spin-off for research & clinical purposes. Since Matrine extracts (from Sophora flavescens) are part of traditional Chinese medicine, Matrine could quickly apply to be part of a cocktail of helpful substances to restore the functionality of ΔF508-CFTR.

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