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Press release

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Tools for data structuring: CandActCFTR Database and the CFTR Life Cycle Map

A DFG-funded project led by Dr. Manuel Nietert from Göttingen and PD. Dr. Frauke Stanke from Hannover has developed a database for substances tested for their effects on CFTR function. The data was compiled in the CandActCFTR database and processed for research purposes. This project also produced the CFTR Life Cycle Map, a computer-readable model with data on the life cycle of the CFTR protein. These tools will help to make data mountains more usable for the identification of CFTR-modulating drug combinations.

Automated compound screenings provide vast amounts of data

Many molecular biology methods have become routine so that scientific experiments nowadays produce a lot of data in a short period. Substance screenings are thus no longer personnel- and time-intensive; robotic arms have long since been pipetting and inserting samples into devices for automated readout processes. Today, some companies specialize in substance screening as service providers and have substance libraries to quickly test thousands or even millions of substances for a specific activity. In addition, many university research groups around the world are searching for and testing substances to make diseases such as cystic fibrosis treatable. In most cases, automated testing of large collections of substances means that the mechanism of action of active substances remains unclear. Understanding the mechanism, however, can be helpful in the further development of the drug as well as in the identification of similar compounds.

CandActCFTR database compiles data from substance screenings

It is almost impossible for an individual researcher to gain an overview of what has already been tested with what kind of result, or to compare data from different approaches, as that would mean knowing hundreds of professional publications and linking their contents. A DFG-funded project led by Dr. Manuel Nietert from Göttingen and PD Dr. Frauke Stanke from Hannover offer a remedy: Using cystic fibrosis research as an example, data from various sources that have been investigated with regard to CFTR function was compiled in the CandActCFTR database and preprocessed for research purposes. Interfaces to chemistry databases allow links to further information, e.g. on chemical structure and possible synonyms, and the list of different names for the same substance is usually surprisingly long.

To prevent misunderstandings, it is therefore important to also use unique identifiers for substances. In CandActCFTR, this is done using the SMILES and InChIKey structure codes. Currently, CandActCFTR contains data on 3,114 different chemical substances (and 268,914 synonyms) from 111 individual scientific publications, categorized, if known, according to their mode of action and interaction with CFTR. And this is just the beginning, as Dr. Manuel Nietert's research group is working to continuously add to the database, and corresponding collaborations are currently being formed (Interested? Contact: CandActCFTR(at)medizin.uni-goettingen.de).

Even supposedly useless data on substances that do not affect the CFTR channel are valuable for the CF research community. Taking them into account is the only way to avoid unnecessary multiple testing and to exclude substance classes, or to gain another piece of the puzzle for a better understanding of the mechanisms of CFTR activation.
The database is freely accessible and a scientific journal article on the CandActCFTR database is now available (see below).

Database

The main goal of the project is the identification of CFTR-modulating drug combinations
The development of the CandActCFTR database is merely a means to an end in the process. The goal of the project is to identify compounds that alone or in combination can help in the maturation or activation of the CFTR protein. To achieve this project goal, it is important to know details about the mode of action of substances - after all, the path from the CFTR gene to the completed CFTR channel in the cell membrane is long and offers various sites as therapeutic targets. In particular, the respective modes of action are of great interest for the development of drug combinations, whose effects synergistically enhance each other.

Liza Vinhoven (Göttingen) has compiled the current knowledge about the lifecycle of the CFTR protein in a human- and computer-readable, model. The systems biology model has been scientifically published as a software tool under the name CFTR Lifecycle Map (see below) and is freely available to all researchers. Currently, 170 different sites are described at the molecular level for which CF-relevant reactions/therapeutic interventions are described in the 221 scientific publications evaluated for this purpose. Again, the validity of the model increases with the number of data fed in. Additions are made on an ongoing basis.

CFTR Lifecycle Map

At the moment, the database and the CFTR Life Cycle Map are being linked. This will facilitate the elucidation of mechanisms of action of substances in the database based on the model, as well as the identification of potential new groups of active substances and their targets in the cell. For this purpose, existing knowledge from databases on drug-protein interactions is being used, but also virtual, computer-based screenings will be performed to identify possible interactions between substances and target proteins.

The CandActCFTR project will use the database and life cycle map to help compile CFTR compound screening data and visualize cellular responses from gene to functioning CFTR channel. In the future, both tools will help identify combinations of CFTR modulators that can be used to treat defects at different points along the pathway of CFTR production, depending on the mutation. Ultimately, these drug combinations can then be tested for their actual efficacy using cell models in the wet lab.

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Nietert M.; Vinhoven L.; Auer F.; Hafkemeyer S.; Stanke F.: Comprehensive analysis of chemical structures that have been tested as CFTR activating substances in a publicly available database CandActCFTR, Frontiers in Pharmacology,2021. https://doi.org/10.3389/fphar.2021.689205

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URL for press release:
https://gepris.dfg.de/gepris/projekt/315063128?context=projekt&task;=showDetail&id;=315063128& Information on the project on DFG website

URL for press release: https://www.youtube.com/watch?v=NMFVTVhcNoI Explanatory video in English