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A biocomputer helps with drug discovery

Discovering drug molecules without side effects is a key challenge when developing a novel medicine. Currently this requires multiple tests, first to check if a molecule has the potential to become a drug, and next to make sure it does not pose danger to patients. Researchers led by Prof. Yaakov Benenson at D-BSSE of ETH Zurich have developed a synthetic biology drug discovery platform that acts as a biological computer simultaneously checking for beneficial and harmful properties of drug candidates and greatly shortening the time to discovery.

Initial discovery and further development of active chemical compounds to treat disease – drug molecules – is a long process. It usually starts with finding a drug target, a molecule that causes the disease. Then, we look for another molecule that interacts with the drug target so as to treat the disease. A common first step in the quest for discovering an active molecule is screening: Up to one million compounds are brought individually in contact with the target to check if they interact. The promising candidates are selected and further tested for interactions with any other molecule in the cell, because these unwanted interactions are the major cause for side effects in patients. Afterwards the compounds are further optimized and a few successful ones are tested in animals and humans. This multi-step procedure is time consuming, lab-intensive and costly. Therefore, testing for the desired activity and the unwanted interactions simultaneously can speed up the development and reduce costs.

Professor Benenson's team of synthetic biologists, headed by Benjamin Haefliger, approached this challenge from the perspective of biological computing – a concept that has been under development in the lab for more than a decade. Biological computers, like ordinary computers, receive and process information from multiple sources in order to provide answers to defined questions. In drug screening, there are two central questions: "Is the compound active?" and "Does the compound affect any other molecules of the cell?" With the help of a biological computer system, these two questions can be answered in a single step. The system monitors the drug target and reports a beneficial effect and its strength; at the same time, it receives information from other molecules in the cell that can be potentially affected by side effects. If these other molecules are also affected, the system reports that a side effect exists. Multiple sources of information feed into this decision process, and even one side effect can trigger the warning.

Benenson's team used miRNA molecules as drug targets. These are short, regulatory RNAs that play an important role in human physiology and disease. After their discovery in the early 2000s, scientists have strived to find ways to treat disease by targeting them. But finding such treatments has proven to be difficult. miRNAs are very similar to each other – they are all built from the same building blocks and produced by the same

molecular machines. Therefore, potent compounds often also interact with other molecules of the cell. The technology works very well with miRNAs - a new but very attractive drug target. However, the basic principle can also be used for other molecules, and this work opens the door to many more assays. Researchers believe that their results represent one of the first outcomes of synthetic biology research that can be directly applied to unmet needs in the real world.

This research is enabled by the NCCR Molecular Systems Engineering and was just published in the journal Nature Communications.

Reference: Haefliger, B., Angelici, B., Prochazka, L. and Benenson, Y., Precision multidimensional assay for high-throughput microRNA drug discovery, Nat. Commun., 2016 (doi: 10.1038/NCOMMS10709).

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About the NCCR Molecular Systems Engineering
Please read more about the interdisciplinary research-project headed by the University of Basel and ETH Zurich and funded by the Swiss National Science Foundation online here: www.nccr-mse.ch or http://www.nccr-mse.ch/en/research/

Upcoming events of the NCCR Molecular Systems Engineering
- 25 Feb. 2016: Basar Molekular at Sud featuring Permi Jhooti and others, 6.20 pm.
- 19 May 2016: SeminBar at Ackermannshof featuring Philipp Holliger, 6pm.
- For more: See our Events Program 2016 online on www.nccr-mse.ch