Novel mathematical framework provides a deeper understanding of how drugs interact

Researchers at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences have developed a new methodology characterizing more precisely how drugs influence each other when combined during treatment. Their analysis of over 30k drug pairs applied to cell lines identified 1,832 interactions between 242 different drugs and sheds new light on how drugs perturb the underlying molecular networks. The findings have now been published in the scientific journal Nature Communications.

(Vienna, 13 November 2019) Combining two or more drugs can be an effective treatment of diverse diseases, such as cancer. Yet, at the same time, the wrong drug combination can cause major side effects. Currently there is no systematic understanding of how different drugs influence each other. Thus, elucidating how two given drugs interact, and whether they have a beneficial effect, would mean a major step towards drug development to treat diseases more effectively in the future.

On a molecular level, drugs cause complex perturbations of various cellular processes in our body. These processes are orchestrated by an intricate network of molecular interactions, the so-called interactome. Over the last decade, numerous studies have revealed a close relationship between the structure of the interactome and the functional organization of the molecular machinery within the cell. This opened exciting opportunities for using network-based approaches to investigate the foundations of both healthy and disease states. Following this trend, Principal Investigator Jörg Menche and his group at CeMM developed a novel mathematical framework for mapping out precisely how different perturbations of the interactome influence each other.

The new study performed by Caldera et al., represents the first general approach to quantifying with precision how drugs interact with each other, based on a mathematical model that considers their high-dimensional effects. Their research reveals that the position of targets of a given drug on the interactome is not random but rather localized within so-called drug modules. They found that the location of a drug module is linked to the specific cell morphological changes induced by the respective treatments, making morphology screens a valuable resource for the investigation of drug interactions. Further they identified various factors that contribute to the emergence of such interactions. Most notably, the distance between two drug modules on the interactome plays a key role: Certain types of interactions are more likely depending on the exact proximity between

the two respective drug modules. If the modules are too far away from each other, it is rather unlikely that an interaction will take place.

"We developed a completely new methodology to classify drug interactions. Previous methods could characterize interactions only as synergistic or antagonistic. Our methodology is able to distinguish 12 distinct interactions types and also reveals the direction of an interaction", says Michael Caldera, first author of the study and PhD student at Jörg Menche's Group.

The study of the Menche group has broadened the understanding of how drugs perturb the human interactome, and what causes drugs to interact. Moreover, the introduced methodology offers the first comprehensive and complete description of any potential outcome that may arise from combining two perturbations. Finally, this methodology could also be applied to address other key challenges, such as dissecting the combined impact of genetic variations or predicting the effect of a drug on a particular disease phenotype. Their research forms a solid base for understanding and developing more effective drug therapies in the future.

The study "Mapping the perturbome network of cellular perturbations" was published in *Nature Communications* on 13 November 2019. DOI: 10.1038/s41467-019-13058-9

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Jörg Menche studied physics in Leipzig, Recife and Berlin. He did his PhD with Reinhard Lipowsky at the Max-Planck-Institute for Colloids and Interfaces in Potsdam (Germany), and was a postdoctoral fellow with Albert-László Barabási at Northeastern University and at the Center for Cancer Systems Biology at Dana Farber Cancer Institute in Boston. He joined CeMM in 2015 as a principal investigator.

The mission of **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is to achieve maximum scientific innovation in molecular medicine to improve healthcare. At CeMM, an international and creative team of scientists and medical doctors pursues free-minded basic life science research in a large and vibrant hospital environment of outstanding medical tradition and practice. CeMM's research is based on post-genomic technologies and focuses on societally important diseases, such as immune disorders and infections, cancer and

metabolic disorders. CeMM operates in a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. The goal of CeMM is to pioneer the science that nurtures the precise, personalized, predictive and preventive medicine of the future. CeMM trains a modern blend of biomedical scientists and is located at the campus of the General Hospital and the Medical University of Vienna.
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