Next-Generation Microscopy

"Pharmacoscopy" enables immunomodulatory drug discovery by analyzing immune cell interactions

A novel microscopy method allows unprecedented insights into the spatial organization and direct interactions of immune cells within blood and other liquid multi-lineage tissues. The assay, called "Pharmacoscopy", developed and patented by scientists from CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, is able to determine the immunomodulatory properties of drugs within large libraries on immune cells in high resolution and high throughput. Introduced in *Nature Chemical Biology*, Pharmacoscopy enables new possibilities for drug discovery, particularly in cancer immunotherapy, personalized medicine, and the research on signaling pathways of the immune system.

(Vienna, April 24, 2016) Our immune system consists of a great variety of cell types fulfilling diverse tasks in monitoring tissue homeostasis to protect against pathogens and to remove damaged cells. To ensure the smooth and controlled functioning of this highly complex system, a fine-tuned coordination is necessary that requires sophisticated communication. For that purpose, immune cells use a wide range of biochemical signaling pathways, activated by soluble proteins or direct cell-cell contacts. Those pathways are also targeted by modern drugs, for instance cancer immunotherapies, that direct the immune response against specific structures or cell types.

The search for new drugs, small molecule or biologicals, that influence the immune system in a desired manner is challenging: immune signaling, often a combination of communication via soluble proteins and direct interaction by cell-cell contacts, is subtle and hard to track in all its nuances. So far, there has been a lack of fast and robust technology to measure the effect of a potential immunomodulatory drug in particular in a cell-cell contact dimension.

By combining state-of-the-art high-throughput fluorescent microscopy with single cell image analysis and novel analysis algorithms, Pharmacoscopy provides a powerful solution. Developed by a group of scientists at CeMM led by Director Giulio Superti-Furga and tested in collaboration with the Medical University of Vienna, Pharmacoscopy can quantify the overall spatial patterning and direct interactions of immune cells within blood with unprecedented speed and accuracy. The method was introduced in *Nature Chemical Biology* (DOI:10.1038/nchembio.2360).

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Combined single cell resolution and fully automated platform control, Pharmacoscopy can test large drug libraries, as available in Stefan Kubicek's PLACEBO (Platform Austria for Chemical Biology) laboratory, for compounds with immunomodulatory potential. "We found that 10% of all approved drugs tested influence the immune system in some way - much of which was not known" states Gregory Vladimer, one of the co-first authors of the study.
With this method, the scientists identified Crizotinib, an FDA approved drug for non-small cell lung cancer, to have a previously unknown immunomodulatory potential: "With Pharmacoscopy, we could track how Crizotinib enables cytotoxic T-cells to attack cancer cells" explains Berend Snijder, the other co-first author. "The compound induces the upregulation of MHC on the surface of cancer cells, a protein complex that is recognized by T-cells and leads to their killing."

"This is the world´s first method to track the modulation of the immune system at high-resolution and high-throughput," says Giulio Superti-Furga, senior author of the study and scientific director of CeMM. "Pharmacoscopy is not only a new and powerful tool for drug discovery; it can also be implemented in basic research by visualizing the effects of signaling molecules on the immune system. In future, Pharmacoscopy should be applied to test individual patient samples on their response to various drugs – a mile stone for the development of a personalized precision medicine."

The study "Global survey of the immunomodulatory potential of common drugs" was published in *Nature Chemical Biology* on April 24, 2016. DOI:10.1038/nchembio.2360

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Giulio Superti-Furga Ph.D., is an Italian citizen working in Vienna, Austria. He performed his undergraduate and graduate studies in Molecular Biology at the University of Zurich, at Genentech Inc. in San Francisco and at the IMP in Vienna. He was a postdoctoral fellow at EMBL Heidelberg and became Team Leader there in 1995. From 1997 to 2000 he served as Guest Professor of

Molecular Biology at the University of Bologna. In 2000, he co-founded the biotech company Cellzome Inc. and served as Scientific Director. Since 2005 he has been Director of CeMM, the Research Center for Molecular Medicine of the Austrian Academy of Sciences, in the middle of the large general hospital campus in Vienna. From 2005 to 2014 Giulio Superti-Furga was a Visiting Professor of Molecular Pharmacology at the Medical University of Vienna, where he was appointed as Professor for Medical Systems Biology in 2015. In Vienna he co-founded the biotechnology companies Haplogen and Allcyte.
As Scientific Director of CeMM, Giulio Superti-Furga has been fostering the precise and preventive medicine of the future by integrating basic research and clinical expertise to pursue pioneering diagnostic and therapeutic approaches. Among his major achievements to date are the elucidation of basic regulatory mechanisms of tyrosine kinases in human cancers, the determination of the precise mechanism of action of several drugs and the discovery of fundamental organization principles of the proteome and lipidome.
He is a member of the Austrian Academy of Sciences, the German Academy of Sciences Leopoldina, the European Molecular Biology Organization (EMBO), the European Academy of Cancer Sciences, and the Academia Europaea. His scientific impact is complemented by his community work. He was serving as Chair of the board of the EMBL Alumni Association from 2008 to 2015, is a founding member of the EU-LIFE consortium (www.eu-life.eu), and has initiated "Genom Austria" (www.genomaustria.at), an educational citizen science project on genome sequencing allowing a wide public to consider and discuss the advantages and challenges of genomic medicine.
He is married to a Viennese and has two children.
http://cemm.at/research/groups/giulio-superti-furga-group/

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. www.cemm.at

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