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Abstract

“Functional Drug-Gene Interaction Screens in Cancer”

Linking the molecular aberrations of cancer to drug responses could guide treatment choice and identify new therapeutic applications. However, there has been no systematic approach for analyzing gene-drug interactions in human cells. We have established a Luminex –based multiplexed assay to study the cellular fitness of a panel of engineered isogenic cancer cells in response to a collection of drugs, enabling the systematic analysis of thousands of gene-drug interactions. Applying this approach to breast cancer we screened a matrix of over 7000 gene-drug interactions, revealing various synthetic lethal interactions and drug resistance mechanisms, some of which were known, thereby validating the method. Importantly, we identify a novel and unexpected mechanism of resistance to PI3K/mTOR inhibitors, which are currently undergoing clinical trials in breast cancer patients. These data illustrate how large-scale chemical genetic screens can reveal therapeutically relevant and unexpected drug-gene interactions.

Biography

Sebastian Nijman obtained his university training in Utrecht where he specialized in Molecular Biology and Biochemistry and he acquired a Masters of Arts degree from the University of Maastricht (Science, Society and Technology Studies). After a “detour” through industry where he was involved in clinical research, he started his PhD in the lab of Rene Bernards at the Netherlands Cancer Institute in Amsterdam. With the help of the first RNAi screen in mammalian cells he assigned a function to the familial tumor suppressor gene CYLD and this work has led to a rational therapeutic approach for treating the tumor syndrome that is caused by mutations in this gene. Sebastian received his post-doctoral training in the lab of Todd Golub at the Broad Institute of Harvard and MIT where he developed new approaches to study drug-gene interactions. In 2007 he started his own group at the Center for Molecular Medicine in Austria where he uses a Luminex-based method to identify synthetic genetic interactions in cancer cells.