IN BRIEF

RNA INTERFERENCE

Lack of interferon response in animals to naked siRNAs.

Heidel, J. D. *et al. Nature Biotech.* 21 Nov 2004 (doi:10.1038/nbt1038)

Small interfering RNAs (siRNAs) are now widely used to silence specific target genes to elucidate their function and to aid in the identification of drug targets. These oligonucleotides also have potential as therapeutics, but one key concern is that they have the potential to elicit an interferon response. Heidel *et al.* show that it is possible to administer naked synthetic siRNAs to mice and downregulate an endogenous or exogenous target without inducing an interferon response.

CARDIOVASCULAR DISEASE

Requirement of JNK2 for scavenger receptor A-mediated foam cell formation in atherogenesis.

Ricci, R. *et al. Science* **306**, 1558–1561 (2004)

The c-Jun N-terminal kinases (JNKs) have been implicated in pro-atherogenic processes. To clarify their role in these processes, Ricci *et al.* used mice that lacked apolipoprotein E (ApoE), which are prone to atherosclerosis, and which also lacked either JNK1 or JNK2. ApoE-deficient mice that lacked JNK2 developed significantly less atherosclerosis than either ApoE-deficient mice or ApoE-deficient mice that also lacked JNK1. Specific inhibition of JNK2 could therefore be a potential therapeutic approach to ameliorate atherosclerosis.

ANTICANCER DRUGS

Small molecule RITA binds to p53, blocks p53–HDM-2 interaction and activates p53 function in tumors.

Issaeva, N. *et al. Nature Med.* 21 Nov 2004 (doi:10.1038/nm1146)

Inhibiting the interaction between the tumour suppressor p53 and HDM2, which leads to degradation of p53, is thought to have potential as a widely applicable and efficient anticancer strategy. However, discovering molecules that disrupt protein–protein interactions is challenging. Rather than searching for HDM2-binding molecules, Issaeva *et al.* screened for compounds that suppressed the growth of tumour cells in a p53-dependent manner, and identified a small molecule that inhibited the p53–HDM2 interaction — RITA — which had antitumour effects in mice.

INFECTIOUS DISEASE

Combating drug-resistant bacteria: small molecule mimics of plasmid incompatibility as antiplasmid compounds.

DeNap, J. C. B. *et al. J. Am. Chem. Soc.* **126**, 15402–15404 (2004)

Many bacteria become resistant to antibiotics through the uptake of a plasmid that encodes resistance-mediating proteins. DeNap *et al.* identified a small molecule that can cause antibiotic-resistant bacteria to eliminate resistance-carrying plasmids (mimicking a natural mechanism known as plasmid incompatibility), which can resensitize bacteria to antibiotics, and which could therefore offer a novel strategy for combating antibiotic resistance.

SCREENING

Single cell screens

An automated microscopy method has been developed that can provide quantitative data relating to changes in phenotype of a single cell in response to different drugs. The method, reported in *Science*, profiles the phenotypic effects of different doses of drugs in cell culture, and was able to both categorize blinded drugs and propose targets for drugs with an unknown mechanism of action. The method provides a complementary approach to existing drug-screening technologies, such as transcript analysis and protein-expression studies.

The study of drug effects on specific cells is often limited to measurements taken at a single dose concentration. Recently, however, the idea of using a combination of imaging techniques to look for particular phenotypes in response to a drug has been proposed. In this study, Perlman and colleagues suggest that using large sets of imaging data could provide a cell profile that is analogous to a gene-expression profile, and they present a method based on measurements of different fluorescent images of cell states that can be used to generate extensive dose–response profiles for many drugs.

Fluorescent probes that represented a range of cell biology (for example, structural proteins, kinases and cell-cycle regulators) were used to study the effects of a test set of 100 compounds, including those with known and unknown mechanisms of action, and a toxin with several known targets. Images were collected of ~8,000 cells per well using automated microscopy, and a set of descriptors recorded for each cell, region and probe, including size, shape and intensity of fluorescent staining.

The authors devised a method of using these descriptors to generate a dosage-dependent profile for each drug. They found that they could readily distinguish drugs with diverse chemical structures that are reported to act at common targets from drugs that work with a different mechanism. Furthermore, as changes in specificity for a target will show as a change in the cell phenotype, but changes in dose will not, the authors developed a titration-invariant similarity score that can profile drugs regardless of the starting dose used in the experiment. The authors speculate that further extension of this method to reflect dependencies between the descriptors used will enable drug profiles to be analysed at a systems level.

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References and links

ORIGINAL RESEARCH PAPER Perlman, Z. E. *et al.* Multidimensional drug profiling by automated microscopy. *Science* **306**, 1194–1198 (2004)