IN BRIEF

LEAD IDENTIFICATION

Better HSP90 inhibitors

Heat shock protein 90 (HSP90) is a potential target for cancer and protein misfolding disorders, yet current inhibitors — such as geldanamycin and derivatives — have hepatotoxicity. Based on the hypothesis that toxicity is due to a reaction of biological nucleophiles at the 19-position of the quinone ring of geldanamycin, this study showed that introducing a substituent at this position blocks the reaction with nucleophiles while causing a conformational switch of the *trans* amide group into the *cis* form that is required for protein binding. These new compounds were less toxic to endothelial and epithelial cells, and also inhibited HSP90 in neuronal and cancer cells.

ORIGINAL RESEARCH PAPER Kitson, R. R. A. *et al.* Synthesis of 19-substituted geldanamycins with altered conformations and their binding to heat shock protein Hsp90. *Nature Chem.* **5**, 307–314 (2013)

ANIMAL MODELS

A speedy route to mutant mice

Generating mouse models that have targeted genetic mutations currently relies on the use of targeting vectors and mutant embryonic stem cells (ESCs). Wefers *et al.* identified a new, quicker way of making mouse models of disease by microinjecting transcription activator-like effector nucleases (TALENs) and synthetic oligodeoxynucleotides into single-cell embryos. The authors created disease-relevant, correctable mutations in the small GTPase RAB38. This technology enabled heterozygous mutant mice to be available within 18 weeks (ESC-based mutant mice can take a year or longer to produce).

ORIGINAL RESEARCH PAPER Wefers, B. *et al.* Direct production of mouse disease models by embryo microinjection of TALENs and oligodeoxynucleotides. *Proc. Natl Acad. Sci. USA* **110**, 3782–3787 (2013)

VACCINES

Bacterial minicells could offer safer vaccines

Bacterial type III protein secretion systems (T3SSs) can present protein antigen to stimulate antigen-specific T cells, and so could be useful for vaccine development. However, current methods require live bacteria. This study engineered the T3SS of *Salmonella enterica* into non-replicating bacterial minicells, which result from aberrant cell division. The engineered system could deliver a specific antigen to the class I antigen presentation pathway, and in mice it primed $CD8^+$ T cells and elicited a protective response against an infectious challenge, suggesting that the T3SS in minicells could be used for vaccine development without the need for live bacteria.

ORIGINAL RESEARCH PAPER Carleton, H. A. *et al.* Engineering the type III secretion system in non-replicating bacterial minicells for antigen delivery. *Nature Commun.* **4**, 1590 (2013)

ANTICOAGULANTS

An antidote to factor Xa inhibitors

Direct inhibitors of factor Xa (fXa) — such as rivaroxaban — are a new class of anticoagulants but lack effective antidotes. In an effort to identify an antidote, Lu *et al.* designed a recombinant, catalytically inactive form of fXa that bound to direct fXa inhibitors as well as antithrombin III (which can inhibit fXa). In animal models of anticoagulation and blood loss, the antidote reversed the effects of the direct fXa inhibitors betrixaban, rivaroxaban and apixaban, and also reversed the effects of the indirect fXa inhibitors enoxaparin and fondaparinux, which indicates that this new antidote has the potential to reverse several fXa inhibitors.

ORIGINAL RESEARCH PAPER Lu, G. *et al.* A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nature Med.* **19**, 446–451 (2013)