**IN BRIEF**

### METABOLIC DISEASE

Mitochondrial circular RNA mitigates NASH

Mitochondrial dysfunction plays a central role in nonalcoholic fatty liver disease (NASH). Now, Zhao et al. report that the mitochondrial circular RNA steatohepatitis-associated circRNA ATP5B regulator (SCAR) is downregulated in liver fibroblasts from patients with NASH. Overexpression of SCAR in NASH fibroblasts blocked mitochondrial permeability transition pore opening, inhibiting mitochondrial reactive oxygen species output and subsequent fibroblast activation. In high-fat diet–fed mice, delivery of SCAR to liver fibroblasts using mitochondria-targeting nanoparticles mitigated insulin resistance and cirrhosis. In patients with NASH, downregulation of SCAR correlated with disease progression.

**ORIGINAL ARTICLE** Zhao, Q. et al. Targeting mitochondria-located circRNA SCAR alleviates NASH via reducing mROS output. Cell https://doi.org/10.1016/j.cell.2020.08.009 (2020)

### CANCER

Delivering CARs with oncolytic viruses

Many solid tumours lack amenable tumour antigens for CAR T cell development. To address this, Park et al. engineered an oncolytic vaccinia virus to express a truncated non-signalling variant of CD19 (OV19t). In vitro, OV19t introduced CD19t on solid tumour cells, which directed activation and cytotoxicity of CD19-CAR T cells. Combination OV19t and CD19-CAR T cell therapy exhibited antitumour efficacy in human tumour xenografts and in an immunocompetent mouse syngeneic tumour model. Analysis of tumours revealed that CD19-CAR T cell–mediated tumour killing promoted viral particle release and infection of tumour cells, while OV19t promoted tumour infiltration of both endogenous and CAR T cells.

**ORIGINAL ARTICLE** Park, A. et al. Effective combination immunotherapy using oncolytic viruses to deliver CAR targets to solid tumors. Sci. Transl. Med. 12, eaaz1863 (2020)

### TYPE 2 DIABETES

Hepatokine improves glucose control

Hepatokines are liver-secreted proteins that regulate liver and systemic metabolism. Gray et al. report that sparc-related modular calcium-binding protein 1 (SMOC1) is a glucose-responsive hepatokine that regulates glucose homeostasis. In mice, acute intraperitoneal administration of SMOC1 improved glycemic control, through suppression of hepatic glucose output. Weekly administration of a stabilized SMOC1-FC fusion protein induced durable beneficial effects on glucose tolerance and insulin action in diabetic mice, and was more effective than metformin. In obese insulin-resistant individuals, plasma SMOC1 was decreased and correlated with insulin sensitivity.

**ORIGINAL ARTICLE** Gray, M. A. et al. SMOC1 is a glucose-responsive hepatokine and therapeutic target for glycemic control. Sci. Transl. Med. 12, eaaz3048 (2020)

### TOXICOLOGY

ACC inhibitors block platelet production

Inhibition of acetyl-CoA carboxylase (ACC), which catalyses the first step of de novo lipogenesis (DNL), is of interest in the treatment of several diseases. However, clinical development of the ACC inhibitor, PF-05175157, was terminated owing to reduced platelet counts. Using an ex vivo cord blood–derived human megakaryocyte (MK) culture system, Kelly et al. show that ACC inhibitors decrease platelet production, and that DNL is essential for formation of the demarcation membrane system (DMS) required for late-stage MK maturation and subsequent platelet formation. While PF-05175157 did not alter platelet counts in rats or dogs, the ACC inhibitor reduced platelets, increased MKs and impaired the DMS in monkeys.

**ORIGINAL ARTICLE** Kelly, K. et al. De novo lipogenesis is essential for platelet production in humans. Nat. Met. https://doi.org/10.1038/s41389-020-00272-9 (2020)

### ANTIMICROBIALS

Building antibiotics block by block

Streptogramins are potent antibiotics against Gram-positive bacteria. However, they are ineffective against bacterial strains — such as certain strains of *Staphylococcus aureus* — that express virginiamycin acetyltransferase (Vat) enzymes, which can deactivate the antibiotic. To overcome resistance conferred by Vat enzymes, Ian Seiple and colleagues have used a modular approach to create synthetic acetylation-resistant streptogramins. One of these compounds is effective against resistant bacterial strains in a mouse model of bacterial infection.

Streptogramins are divided in two groups, A and B. Group A streptogramins, such as the natural product Virginiamicin M2 (VM2), bind to a site of the bacterial ribosome called the peptidyl transferase centre, which then promotes the binding of group B streptogramins to an adjacent region. Binding to both parts of the ribosome results in synergistic inhibition of bacterial protein synthesis.

VatA enzymes can deactivate group A streptogramins by transferring an acetyl group to an alcohol group in position C14, which prevents binding to the ribosome, blocking antibiotic activity. Unfortunately, previous efforts to synthesize active derivatives of group A streptogramins that could avoid acetylation have been unsuccessful.

To engineer group A streptogramins that could avoid Vat deactivation while maintaining ribosomal binding, the authors first used cryo-electron microscopy to obtain structures of VM2 derivatives bound to *Escherichia coli* ribosomes. From these structures, and from mutagenesis studies, they hypothesized that modifications at the C4 position of VM2 would disrupt acetylation by Vat enzymes while maintaining binding to the ribosome. Therefore, structural modifications of this position might overcome Vat resistance without affecting antibiotic activity. However, this residue could not readily be modified through semisynthesis without affecting other parts of the molecule. Therefore, an alternative approach was required.

The authors developed a pipeline for the modular synthesis of group A streptogramins based on the parent scaffold VM2 and convergent assembly of individually diversifiable chemical building blocks. The approach involves the synthesis of two halves of similar complexity, which are then joined by amide bond coupling in a total of eleven steps. By changing the building blocks, they prepared 18 analogues, and then selected some of these for further modifications, such as modifying C3, obtaining a total of 62 compounds that they then tested against a panel of 20 pathogens.

Replacement of the C4 methyl group with a larger allyl group resulted in a new compound, compound 47, with potent activity against a series of streptogramin-resistant bacterial strains.

Finally, they tested the efficacy of this compound in a mouse model of infection using streptogramin-resistant *S. aureus*. Compound 47 showed significant reduction in bacterial load even in the absence of a group B streptogramin partner.

This study shows the potential of modular chemical synthesis to develop derivatives of complex natural products. This could enable efforts to improve characteristics of known antibiotics that have limited their potential as drug candidates.

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**ORIGINAL ARTICLE** Li, Q. et al. Synthetic group A streptogramin antibiotics that overcome Vat resistance. Nature 586, 145–150 (2020)