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IN BRIEF

AGING

Promoting NAD^+ production

Accumulating evidence indicates that NAD^+ — a coenzyme for several enzymes, with a critical role in mitochondrial energy production — confers protection against ageing and numerous diseases. Using *Caenorhabditis elegans* and cell lines, Katsyuba et al. identify α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD) as a key regulator of the de novo NAD^+ synthesis pathway. Knockdown of ACMSD boosted NAD^+ levels, increased sirtuin 1 activity and enhanced mitochondrial function. In mice, the ACMSD inhibitors TES-991 and TES-1025 increased tissue NAD^+ levels and protected hepatic and renal function in models of nonalcoholic fatty liver disease and acute kidney injury, respectively.

ORIGINAL ARTICLE Katsyuba, E. et al. De novo NAD+ synthesis enhances mitochondrial function and improves health. *Nature* https://doi.org/10.1038/s41586-018-0645-6 (2018)

DRUG REPURPOSING

Heart failure drug effective in medulloblastoma

New therapies to improve survival and limit treatment-related complications in medulloblastoma (MB) are needed. Using a drug functional network (DFN)-based drug repositioning approach, Huang et al. integrated genomic profiles from patients with groups 3 and 4 MB with data from human cancer signalling pathway resources and the gene expression profiles of 1309 drugs. This analysis identified cardiac glycoside family members (used to treat heart failure) as potential inhibitors of cancer driver signalling in groups 3 and 4 MB. In orthotopic patient-derived xenograft models of these cancers, intraperitoneal administration of digoxin significantly improved survival.

ORIGINAL ARTICLE Huang, L. et al. Systems biology-based drug repositioning identifies digoxin as a potential therapy for groups 3 and 4 medulloblastoma. *Sci. Transl Med.* **10**, eaat0150 (2018)

CANCER

Redirecting T cell activity in solid tumours

In comparison to haematological malignancies, redirecting T cell activity to eradicate solid tumours has proved challenging, primarily owing to the lack of tumour-restricted antigens. Here, Slaga et al. develop an anti-HER2/CD3 T cell–dependent bispecific (TDB) antibody that selectively targets HER2-overexpressing tumour cells relative to healthy cells, owing to the presence of two low-affinity anti-HER2 Fab arms. A single intravenous dose of the antibody potently induced regression of HER2-overexpressing tumours in mouse xenograft models. Importantly, the antibody displayed limited pharmacological activity in cynomolgus monkey tissues and was well-tolerated.

ORIGINAL ARTICLE Slaga, D. et al. Avidity-based binding to HER2 results in selective killing of HER2-overexpressing cells by anti-HER2/CD3. *Sci. Transl Med.* **10**, eaat5775 (2018)

TYPE 2 DIABETES

Microbial metabolite impairs insulin signaling

Dysregulation of the gut microbiota and microbially derived metabolite production has been associated with metabolic disorders. Using metabolomics, Koh et al. identify levels of the amino acid-derived metabolite imidazole propionate to be elevated in the portal and peripheral blood of subjects with type 2 diabetes. Using an in vitro gut simulator, imidazole propionate was found to be a histidine-derived metabolite produced from microbial communities specific to subjects with type 2 diabetes. When injected into mice, imidazole propionate impaired glucose tolerance and insulin signalling.

ORIGINAL ARTICLE Koh, A. et al. Microbially produced imidazole propionate impairs insulin signaling through mTORC1. *Cell* **175**, 947–961.e17 (2018)