IN BRIEF

INFECTIOUS DISEASES

Towards a universal flu vaccine

A 'universal' vaccine, that broadly protects against all influenza A viruses (IAVs), is urgently needed. Park et al. now demonstrate that intramuscular or intranasal delivery of an inactivated multivalent IAV vaccine cocktail (composed of four β-propiolactone–inactivated low pathogenicity avian IAV subtypes of H1N9, H3N8, H5N1, and H7N3) protects against multiple IAV hemagglutinin and neuraminidase subtypes in both mice and ferrets, including antigenically variable and heterosubtypic avian, swine, and human viruses. Vaccinated animals displayed reduced viral titres, lung pathology and inflammatory responses, without any signs of toxicity. A phase I safety and immunogenicity study of the vaccine has been initiated.

ORIGINAL ARTICLE Park, J. et al. An inactivated multivalent influenza A virus vaccine is broadly protective in mice and ferrets. *Sci. Transl Med.* **14**, eabo2167 (2022)

RNA THERAPEUTICS

Improving circular RNA protein yields

RNA circularization has the potential to extend the durability of RNA-based therapeutics. Here, Chen et al. create a circular RNA (circRNA) modular cloning platform that enables testing of numerous sequence variations and independent optimization of multiple parameters. Five factors — vector topology, 5′ and 3′ untranslated regions, internal ribosome entry sites and synthetic aptamers — controlling circRNA translation were systematically dissected. Optimizing these elements improved circRNA protein yields by several hundred-fold, generating circRNAs which produced more protein than mRNAs in vitro, and exhibited more durable translation and functional activity in mice.

ORIGINAL ARTICLE Chen, R. et al. Engineering circular RNA for enhanced proteinproduction. *Nat. Biotech.* https://doi.org/10.1038/s41587-022-01393-0 (2022)

CANCER

Targeting ALDH1B1 in colorectal cancer

Overexpression of aldehyde dehydrogenase (ALDH) is associated with cancer initiation, progression and resistance to therapy. Feng et al. now report the discovery of small-molecule inhibitors of ALDH1B1, a mitochondrial ALDH isoform which promotes colorectal cancer. Building on previous findings, they develop bicyclic imidazolium ALDH1B1 inhibitors. Replacing the constitutively cationic scaffold of the imidazoliums with a bicyclic guanidine eliminated off-target mitochondrial toxicity. These guanidine derivatives non-competitively target the substrate binding pocket to potently and selectively inhibit ALDH1B1, suppressing growth of 5-fluorouracil-resistant colon cancer spheroids and patient-derived organoids.

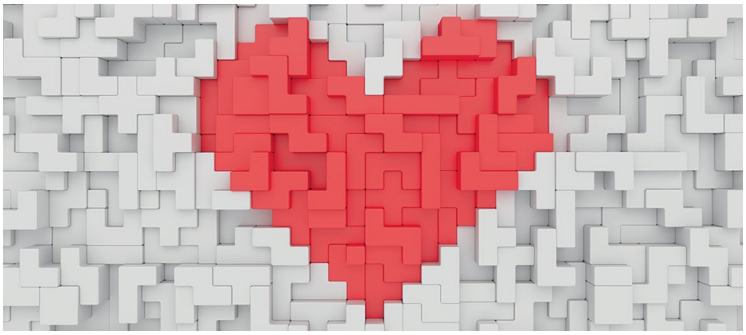
ORIGINAL ARTICLE Feng, Z. et al. Targeting colorectal cancer with small-molecule inhibitors of ALDH1B1. *Nat. Chem. Bio.* https://doi.org/10.1038/s41589-022-01048-w (2022)

CARDIOVASCULAR DISEASES

Inhibiting IgE in pulmonary hypertension

The mechanisms mediating the pulmonary vascular remodelling that occurs in pulmonary arterial hypertension (PAH) remain unclear. Here, Shu et al. identify high serum IgE levels in patients with PAH and in mouse and rat models of pulmonary hypertension (PH). Antibody-mediated IgE blockade prevented the development of PH in mice and rats. Mechanistically, IgE promoted vascular muscularization by binding with FcεRIα, activating mast cells and promoting the release of IL-6 and IL-13. The clinically approved anti-IgE monoclonal antibody omalizumab ameliorated established PH in rats.

ORIGINAL ARTICLE Shu, T. et al. Inhibition of immunoglobulin E attenuates pulmonary hypertension. *Nat. Cardiovasc. Res.* https://doi.org/10.1038/s44161-022-00095-9 (2022)



Credit: JuSun/E+/Getty

CARDIOVASCULAR DISEASE

Loss of Y chromosome promotes cardiac fibrosis

Mosaic loss of Y chromosome (mLOY) arises when the male-specific chromosome is lost in adult stem cells and their progeny. The frequency of mLOY in haematopoietic stem cells increases with age and is associated with an elevated risk of mortality and age-related diseases, including heart failure. However, the existence of a causal relationship had not been shown. Now, a study in *Science* reports that haematopoietic mLOY skews macrophages to a profibrotic phenotype, and inhibiting transforming growth factor-β (TGF-β) signalling lessens cardiac dysfunction in mouse models.

The Y chromosome is small and contains few genes. Relatively little is known about Y chromosome function beyond sex determination and spermatogenesis.

In the current study, Sano et al. used lentivirus-delivered CRISPR-Cas9 to ablate the Y chromosome in bone marrow cells, which they transplanted into irradiated wild-type mice. The inherent inefficiency of lentivirus transduction resulted in mLOY (as opposed to complete loss of Y chromosome) in circulating white blood cells, mimicking the chimerism seen in adult men.

The mice had a shorter lifespan than controls, and developed cardiomyopathy, kidney and lung fibrosis, and deficits in working memory.

To corroborate these findings in humans, the authors analysed prospective data from the UK Biobank. They found that mLOY in >40% of leukocytes increased the risk of death by approximately one-third over an average of 11.5 years of follow-up.

To investigate the possible mechanisms at play, Sano et al. used transverse aortic constriction (TAC) as a model of heart failure. mLOY mice showed greater decline in cardiac function and more myocardial fibrosis than wild-type mice following TAC.

Bulk and single-cell analysis revealed mLOY skewed macrophages towards a fibrotic phenotype, promoting expression of TGF-β by these cells. Fluorescence immunohistochemistry highlighted increased TGF-β in other myocardial cells and the extracellular matrix. The findings suggest a feedforward signalling loop in which TGF-β secreted by mLOY macrophages that have trafficked to the heart in turn stimulates production of TGF-β by tissue-resident cells, promoting cardiac fibrosis.

Last, administration of a TGF-β-specific antibody reduced levels of TAC-induced cardiac dysfunction in mLOY mice towards levels seen in control mice. The antibody treatment suppressed mLOY-associated increases in fibroblast number and extracellular matrix deposition in the heart.

Together, these findings highlight a crucial role of the Y chromosome in regulating innate immune cell function that warrants further study. The authors note that ongoing efforts to treat heart failure, idiopathic pulmonary fibrosis and some cancers with antifibrotic agents might be particularly beneficial in patient subpopulations with haematopoietic mLOY.

Katie Kingwell

ORIGINAL ARTICLE Sano, S. et al. Hematopoietic loss of Y chromosome leads to cardiac fibrosis and heart failure mortality. *Science* **377**, 292–297 (2022)