IN BRIEF

INFECTIOUS DISEASE

Sorafenib analogue combats MRSA

New strategies to tackle methicillin-resistant *Staphylococcus aureus* (MRSA) are urgently needed. By screening 232 commercial kinase inhibitors, Le et al. found that the cancer agent sorafenib has antibacterial activity against MRSA strains. A structure–activity relationship study enabled development of the more potent analogue PK150, which targeted two essential bacterial proteins: demethylmenaquinone methyltransferase and signal peptidase IB. PK150 rapidly killed exponentially growing *S. aureus*, reduced persisters and established biofilms, and did not induce in vitro resistance. In mouse models of MRSA infection, oral dosing of PK150 was as effective as intraperitoneal injection of the marketed antibiotic levofloxacin.

ORIGINAL ARTICLE Le, O. M. et al. Repurposing human kinase inhibitors to create an antibiotic active against drug-resistant *Staphylococcus aureus*, persisters and biofilms. *Nat. Chem.* https://doi.org/10.1038/s41557-019-0378-7 (2019)

WOUND HEALING

Hydrogel fights infection and inflammation

There is a need for more effective treatments to promote wound healing. Now, Puthia et al. have developed a novel hydrogel formulation incorporating the antimicrobial peptide TCP-25, which exhibits dual antibacterial and anti-inflammatory activity. The TCP-25 hydrogel killed *Staphylococcus aureus* and *Pseudomonas aeruginosa* in vitro and in experimental mouse models of subcutaneous infection, and also reduced LPS-induced local inflammatory responses in mice, without any signs of toxicity. In a pig wound model, the hydrogel reduced concentrations of proinflammatory cytokines and was more effective in treating and preventing *S. aureus* infection than the commonly used wound treatments Mepilex Ag and Prontosan.

ORIGINAL ARTICLE Puthia, M. et al. A dual-action peptide-containing hydrogel targets wound infection and inflammation. *Sci. Transl Med.* **12**, eaax6601 (2020)

CANCER

Improving immunotherapy

Although immune checkpoint blockade (ICB) — such as anti- PD-1 therapy — has yielded promising results, many cancer patients do not respond. Two new papers now report combination approaches to improve ICB response. Zhang et al. report that in small-cell lung cancer (SCLC) cell lines, their previously identified inhibitor of CDK7, YKL-5-124, disrupts cell-cycle progression and causes DNA replicative stress and genome instability, while activating immune-response signalling. In mouse SCLC models, these effects provoked a robust immune surveillance, leading to T cell-mediated tumour control. YKL-5-124 enhanced the tumour response to anti-PD-1 therapy and increased survival, without toxicity. Adding YKL-5-124 and anti-PD-1 to standard chemotherapy further improved tumour response, leading to the longest survival. Meanwhile, to identify drivers of resistance to immunotherapy, Abril-Rodriguez et al. generated transcriptome data from biopsies from 41 patients with advanced melanoma treated with a PD-1-blocking antibody. Expression of p21-activated kinase 4 (PAK4) was enriched in non-responding tumour biopsies with low immune cell infiltration. Genetic and pharmacological PAK4 inhibition altered WNT–β-catenin signalling, increased intratumoural T cell infiltration and sensitized tumours to PD-1 blockade in mouse models.

ORIGINAL ARTICLES Zhang, H. et al. CDK7 inhibition potentiates genome instability triggering anti-tumor immunity in small cell lung cancer. *Cancer Cell* **37**, 1–18 (2020) | Abril-Rodriguez, G. et al. PAK4 inhibition improves PD-1 blockade immunotherapy. *Nat. Cancer* https://doi.org/10.1038/s43018-019-0003-0 (2019)

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CARDIOVASCULAR DISEASE

Saving hearts with HDAC inhibition

Heart failure (HF) with preserved ejection fraction (HFpEF), which is characterized by left ventricular (LV) diastolic dysfunction, has a 5-year survival rate as low as 50%, representing a great unmet therapeutic need. However, the lack of HFpEF models that capture key characteristics such as pulmonary dysfunction has limited the ability to test new therapies. Using a novel large-animal HFpEF model, Wallner et al. report that broad inhibition of histone deacetylase (HDAC) activity results in cardiopulmonary function improvement.

Their study is based on two recent advances by authors in the group. One is the development of a feline model of HFpEF involving loose aortic banding, which recapitulates key features of the human disease, including structural changes and pulmonary dysfunction. The other is the demonstration that HDAC inhibition can ameliorate LV diastolic dysfunction in mouse models of HF by potentiating myofibril relaxation through a non-genomic mechanism.

In this latest study, the authors evaluated whether HDAC inhibition has similar effects in their larger feline HFpEF model. Treatment with the FDA-approved HDAC inhibitor, suberoylanilide hydroxamic acid (SAHA), resulted in robust anti-hypertrophic effects, which included blunted and slight reversed pressure-induced LV hypertrophy, a significant decrease in LV wall thickness, as well as decreased left atrial (LA) size and volume with significantly improved LA function; and lowered LV filling pressures.

At 4 months after banding, SAHA mediated an overall improvement in both systolic and diastolic function. Treatment led to improved isovolumic relaxation in addition to a significant reduction in both LV end-diastolic pressure and mean pulmonary arterial pressure.

Notably, in this feline HFpEF model, SAHA improved lung compliance and overall gas-exchange functions, while attenuating negative morphological changes. The authors suggest this is probably due to normalized LV filling pressures.

SAHA treatment also promoted a switch in skeletal muscle fibre composition, increasing the percentage of type 1 muscle fibres, which is typically reduced in patients with HFpEF. Type 1 fibres have a high oxidative capacity, and HDAC inhibition probably directly modifies mitochondrial function, as observed in SAHA-treated HeLa cells and adult feline ventricular myocytes. Corroborating these findings, SAHA treatment altered mitochondrial metabolism in the feline model through post-translational modifications, which were confirmed by acetylation proteomics.

Overall, treatment with an HDAC inhibitor could restore both impaired myofibril relaxation and energy supply in the failing heart by improving cellular metabolic function. The authors are now evaluating the effects of HDAC inhibition on cardiac contractility and relaxation in human atrial and ventricular myocardium, which could provide further data needed to support the initiation of a clinical trial.

Stacey-Lynn Paiva

ORIGINAL ARTICLE Wallner, M. et al. HDAC inhibition improves cardiopulmonary function in a feline model of diastolic dysfunction. *Sci. Transl Med.* **12**, eaay7205 (2020)
RELATED ARTICLES Wallner, M. et al. A feline HFpEF model with pulmonary hypertension and compromised pulmonary function. *Sci. Rep.* **7**, 16587 (2017) | Jeong, M. Y. et al. Histone deacetylase activity governs diastolic dysfunction through a nongenomic mechanism. *Sci. Transl Med.* **10**, eaao0144 (2018)