

## ANTIVIRAL IMMUNITY

## Immune-boost for the elderly

Mechanistic target of rapamycin (mTOR) has long been known to play a role in ageing and longevity. Now, reporting in *Science Translational Medicine*, Mannick and colleagues show that treatment with a low dose of a combination of drugs that inhibit TORC1, a multi-protein complex that contains mTOR, can enhance responses to flu vaccination and decrease overall infection rates in elderly humans.

In a randomized, double-blind placebo-controlled phase IIa clinical trial, 264 elderly volunteers (aged 65 and over) were given a combination of TORC1 inhibitors (BEZ235 and/or RAD001). Subjects received monotherapy, combination therapy or placebo, and were treated daily for 6 weeks. After a 2-week interval, they were given a seasonal influenza vaccine and followed for 10 months.

Only the group receiving the combination therapy met the primary end point, defined as a serological response to vaccination

that had previously been associated with a decrease in subsequent influenza virus infection. This group also had the lowest rate of overall self-reported infections, although the BEZ235 monotherapy group also had a significant reduction in infections (1.49 for combination therapy and 1.61 for BEZ235 monotherapy, compared with 2.41 for placebo).

To test whether the improved response correlated with more complete TORC1 inhibition, phosphorylation of the TORC1 substrates S6K, S6 and 4EBP1 was measured in the livers of rats that received dose equivalents of the drugs tested in humans. Indeed, only the combination therapy significantly inhibited all three downstream nodes.

Whole-blood gene expression analysis revealed an upregulation of pathways related to interferon signalling in the volunteers who received the combination therapy. Among the most highly upregulated genes was a subset of type 1



Credit: S. Bradbrook/  
Springer Nature Limited

“ Whole-blood gene expression ... revealed an upregulation of pathways related to interferon signalling ”

interferon-induced genes that have a crucial role in antiviral responses.

The authors hypothesize that drugs that upregulate antiviral genes may be more effective in preventing infection than drugs targeted at individual viruses. Moreover, they speculate that immune-enhancing drugs may also benefit cancer immunosurveillance and the clearance of senescent cells, which contribute to organ dysfunction during ageing — and therefore may have pleiotropic health benefits in the elderly.

Alexandra Flemming

**ORIGINAL ARTICLE** Mannick, J. B. et al. TORC1 inhibition enhances immune function and reduces infections in the elderly. *Sci. Transl. Med.* **10**, eaaq1564 (2018)