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INFECTION

# Unlocking the 'crypto' drug cabinet

Diarrhoeal disease remains one of the major contributors to global child mortality. KDU731, a pyrazolopyridine analogue, has now been identified as a promising drug candidate for cryptosporidiosis, one of the leading causes of childhood infectious diarrhoea.

Despite its role in the burden of diarrhoeal disease, combating *Cryptosporidium* infection remains a challenge. The only approved treatment has limited efficacy in certain populations, such as immunocompromised patients and those with malnutrition, and the parasite itself is difficult to work with in laboratory research settings.

Manjunatha *et al.* screened a library of 6,220 compounds with antiparasitic activity and developed transgenic parasites and mouse models of infection as part of their drug discovery process. They first identified pyrazolopyridine analogues as inhibitors of both *Cryptosporidium hominis* and *C. parvum* infection *in vitro*, the two major pathogens causing cryptosporidiosis in humans, identifying KDU731 in particular as a potent inhibitor of *Cryptosporidium* phosphatidylinositol-4-OH kinase enzymatic activity.

The researchers engineered transgenic parasites that expressed a luciferase reporter and could be tracked using whole-animal imaging, enabling easier quantification of parasite load in mouse models. Oral treatment with KDU731 in immunocompromised mice (IFNγ-knockouts) infected with transgenic *C. parvum* led to a marked reduction in parasite load and oocyst shedding in faeces. A similar reduction in faecal oocyst shedding upon KDU731 treatment was observed in neonatal calves infected with *C. parvum* (a model resembling human infection), alongside quick resolution of diarrhoea and decreased levels of dehydration.

"Now that we have powerful genetic tools and reporters for this important intestinal pathogen the doors are wide open," notes author Boris Striepen, providing further avenues of research into *Cryptosporidium*. Striepen is hopeful that this new drug candidate can move towards human clinical trials, although additional compounds and targets are needed. "While KDU731 is an excellent drug candidate, continued efforts to build and expand the pipeline are needed".

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**ORIGINAL ARTICLE** Manjunatha, U. H. *et al.* A *Cryptosporidium* PI(4)K inhibitor is a drug candidate for cryptosporidiosis. *Nature* http://dx.doi.org/10.1038/nature22337 (2017)