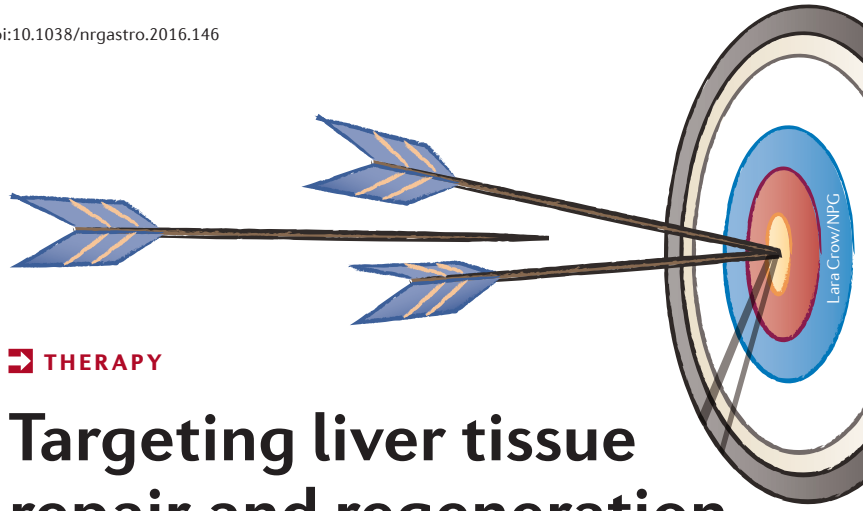
Nature Reviews Gastroenterology & Hepatology | Published online 8 Sep 2016; doi:10.1038/nrgastro.2016.146



THERAPY

Targeting liver tissue repair and regeneration

A new small-molecule inhibitor targeting kinases critical for Hippo pathway signalling has been shown to promote liver repair and regeneration in experimental models of both acute and chronic liver injury. The findings, reported in *Science Translational Medicine*, highlight a potential pharmacological strategy to combat liver damage by boosting repair and regeneration.

"Most regenerative medicine strategies have focused on delivering biomaterials and cells, yet there is the untapped potential for drug-induced regeneration with good specificity and safety profiles," explains author Dawang Zhou. The Hippo pathway is a key regulator of organ size and regeneration and the kinases MST1 (also known as serine/threonine-protein kinase 4) and MST2 (also known as serine/threonine-protein kinase 3) are crucial components of this pathway with a role in control of organ growth: liver-specific deletion of MST1/2 has been shown to result in overgrowth and increased cell proliferation. Zhou and colleagues therefore reasoned that therapeutically targeting MST1/2 kinase activity could promote tissue repair after injury.

Using an ELISA-based high-throughput screen (searching ~3,000 compounds), the investigators identified a reversible and selective MST1/2 kinase inhibitor called XMU-MP-1. This particular small molecule had the best inhibitory activity of all the compounds screened, and analysis of cocrystal structures of protein–inhibitor complexes verified that XMU-MP-1 targets MST1/2.

Next, the researchers confirmed that XMU-MP-1 promoted liver repair and regeneration *in vivo* in mice. Wild-type mice treated daily for 2 months with XMU-MP-1 had ~20–30% increase in liver:bodyweight ratios, with no reported adverse effects, including no detectable signs of cancerous growth. Crucially, XMU-MP1 (1 mg/kg daily for 1 week) promoted liver repair and regeneration and attenuated liver disease in four different models of acute and chronic liver injury (partial hepatectomy, paracetamol-induced injury, bile duct ligation and carbon tetrachloride administration). Interestingly, the MST1/2 inhibitor promoted regeneration in intestinal tissue, protecting mice from experimental colitis, and boosted the repopulation of human hepatocytes in mice.

"The lack of effective methods to improve engraftment and proliferation of donor hepatocytes after transplantation is a major challenge in human hepatocyte transplantation," explains Zhou, "our data suggest that targeting Hippo kinases MST1/2 by XMU-MP-1 might support hepatocyte expansion after transplantation in patients". This new agent could also be used to study the mechanisms of other disease and organ pathobiology induced by the Hippo signalling pathway.

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ORIGINAL ARTICLE Fan, F *et al.* Pharmacological targeting of kinases MST1 and MST2 augments tissue repair and regeneration. *Sci. Transl. Med.* **352**, 352ra108 (2016)