RESEARCH HIGHLIGHT

Prometheus 2.0: drug-induced liver regeneration arising

Jan S. Tchorz[1]✉

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In a recent publication in *Cell*, a multidisciplinary academic drug discovery team, with its spin-off HepaRegeniX, published a first-in-class small molecule MKK4 inhibitor (HRX215) with remarkable efficacy in multiple preclinical liver regeneration models and positive first-in-human data. Its potential to prevent liver failure and boost regeneration may provide a novel therapeutic avenue for many patients with liver disease.

The regenerative capacity of the liver is known since the myth of Prometheus. While healthy human livers rapidly regenerate in response to mild to moderate acute injury, impaired liver regeneration in patients with severe acute or chronic liver injury often results in lethal liver failure.[1] The increasing incidence of severe liver diseases worldwide accounts for over 2 million deaths annually[2] and liver transplantation remains the only curative treatment option for patients with end-stage liver disease. Unfortunately, many patients face liver failure and die while on the waitlist due to the dramatic shortage in suitable grafts. While living donor or split liver transplantations could significantly increase the number of life-saving transplantations, insufficient functional hepatic mass in small grafts often fails to meet the post-operative metabolic needs of the recipient. Similarly, post-surgical liver failure limits the extension of life-saving hepatectomies in patients with colorectal liver metastases or primary liver tumors.[3] While diverse therapeutic concepts to promote liver regeneration exist,[1,3,4] successful translation into the clinic is missing to date.

About a decade ago, Lars Zender and his team identified MKK4 as a potential therapeutic target for enhancing liver regeneration in a direct in vivo shRNA screen.[5] Due to the presumably slow-onset and long-duration kinetics of therapeutic siRNAs, they teamed up with experienced drug hunters Wolfgang Albrecht and Stefan Laufer, and founded HepaRegeniX, to develop selective small-molecule MKK4 inhibitors.[6] Zwirner et al.[7] now published the generation, preclinical characterization and phase I clinical data for HRX215, their first-in-class clinical MKK4 inhibitor candidate.

The publication is starting off with genetic in vivo validation, suggesting tolerability and safety of prolonged systemic MKK4 inhibition, followed by an exciting medicinal chemistry journey leading to the discovery of HRX215. Lacking an exploitable ATP-binding pocket model and sizeable compound libraries found in pharmaceutical companies, they took a smart shortcut by leveraging the off-target MKK4 inhibition found with the clinically approved $BRAF_{V600E}$ inhibitor vemurafenib. In an iterative medicinal chemistry effort, they improved potency against MKK4 and removed the affinity to the RAF kinase motif, while also dialing out JNK1 and MKK7 inhibition to preserve the pro-regenerative effect associated with MKK4 inhibition. NMR-enabled structure-activity relationship-driven modifications resulted in the lead molecule HRX215.[7]

Given its excellent oral bioavailability and favorable pharmacokinetics profile, the authors showcased the preclinical efficacy of HRX215 in several liver injury models. Drug-mediated MKK4 inhibition did not only promote liver regrowth in mice, but Scott Nyberg's surgical team also successfully established preclinical proof-of-concept demonstrating improved survival and reduced post-surgical liver failure in a lethal 85% pig hepatectomy model. Investigational new drug (IND)-enabling Good Laboratory Practice (GLP) toxicity studies confirmed excellent tolerability and safety of HRX215. The placebo-controlled exploratory phase I first-in-human study demonstrated favorable dose-dependent pharmacokinetics and safety of HRX215, paving the way for future phase II efficacy studies.

Other groups are developing cell therapies to restore liver function in hereditary liver diseases, to restore liver function in various injury settings or to boost liver regeneration by leveraging the pro-regenerative factors secreted from transplanted cells.[1,4] However, the expansion, transplantation and engraftment of cells still pose challenges for the development of regenerative therapies when compared to the ease of swallowing a pill restoring Prometheus's power. Several studies demonstrated preclinical liver regeneration efficacy of experimental drugs targeting cMET/HGF, nuclear hormone receptors, IL6, WNT/β-catenin or YAP signaling.[3] However, clinical translation of these findings is largely missing, also due to adverse systemic effects and cancer risk associated with some potential regenerative therapies. For example, activation of WNT/β-catenin signaling in mice using untargeted RSPO1-fc enhanced liver regeneration following partial hepatectomy,[8] but impaired metabolic zonation and function in the liver.[9] Moreover, prolonged WNT/β-catenin pathway activation in transgenic mice induced liver tumor formation.[9] Activating YAP signaling using the selective small-molecule LATS kinase inhibitor NIBR-LTSi promoted hepatocyte proliferation across all hepatic zones but failed to improve survival in an 86% extended hepatectomy mouse model, likely due to systemic YAP activation and resulting severe hyperplasia and cellular dedifferentiation in extrahepatic tissues.[10] These examples illustrate the challenges the field is facing, largely owing to the multimodal mechanisms of action of the regenerative pathways, lack of tissue selectivity and risk for tumor development.

This is where MKK4 as a target seems to excel other approaches. The unique mechanism of action associated with MKK4 inhibition, rewiring stress-activated protein kinase signaling in hepatocytes via the pro-regenerative MKK7-JNK1-ATF2/ELK1 route, seems to surpass many potential challenges. First, MKK4 inhibition has little to no effect on hepatocyte proliferation in healthy livers, but only exerts its pro-regenerative potential when needed. Second, there seems to be a protective roof blocking HRX215 from pushing

[1]Biomedical Research, Novartis Pharma AG, Basel, Switzerland. ✉email: jan.tchorz@novartis.com

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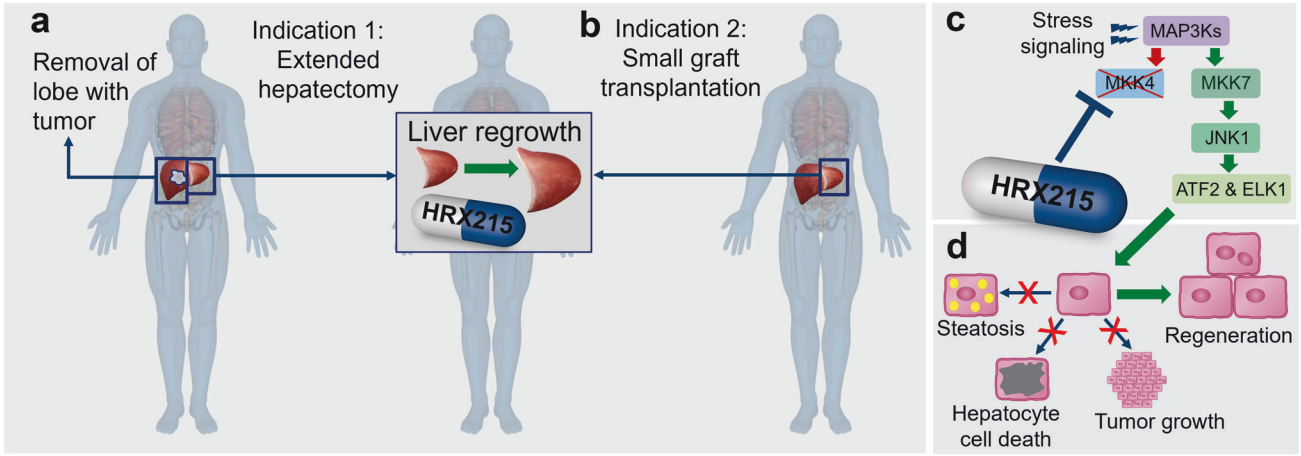

Fig. 1 Translating therapeutic MKK4 inhibition into the clinic with HRX215. a, **b** Promoting liver regrowth could prevent post-surgical liver failure following extended hepatectomies to resect tumors (**a**) or following small graft transplantation (**b**). **c** HRX215-mediated MKK4 inhibition rewires stress signaling via the pro-regenerative MKK7-JNK1-ATF2/ELK1 route. **d** HRX215 promotes hepatocyte proliferation and regeneration, while reducing steatosis, apoptosis and tumor growth.

proliferation beyond physiological levels. Third, HRX215 did not increase or accelerate tumor development in a NASH-HCC model but even showed a tendency towards reducing tumor growth. Altogether, this balanced efficacy and safety profile renders HRX215 as a first-in-class drug with the potential to prevent liver failure in patients with large resections or small graft transplantations (Fig. 1). This could not only enable many more life-saving liver transplantations but also increase the possibilities for curative tumor resection in the liver.

A major cause for liver-related deaths is acute on chronic liver failure, specifically acute alcoholic hepatitis.[2] These patients suffer from hepatocyte loss, liver failure and impaired metabolic function causing toxic ammonia levels. Importantly, HRX215 significantly reduced ammonia levels and prevented liver failure in the 85% pig hepatectomy model. It is therefore possible that MKK4 inhibition, alone or in combination with anti-inflammatory therapies, also helps a broader group of patients with acute on chronic liver failure. More work is required to follow up on the anti-steatotic and potential anti-fibrotic effects of HRX215, possibly highlighting additional therapeutic benefits associated with MKK4 inhibition.

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COMPETING INTERESTS

J.S.T. is employed by and holds shares of Novartis Pharma AG but declares no conflict of interest associated with this research highlight.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Jan S. Tchorz.